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Effect of Partially Fluorinated *N*-Alkyl-Substituted Piperidine-2-carboxamides on Pharmacologically Relevant Properties

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The modulation of pharmacologically relevant properties of *N*-alkyl-piperidine-2-carboxamides was studied by selective introduction of 1–3 fluorine atoms into the *n*-propyl and *n*-butyl side chains of the local anesthetics ropivacaine and levobupivacaine. The basicity modulation by nearby fluorine substituents is essentially additive and exhibits an exponential attenuation as a function of topological distance between fluorine and the basic center. The intrinsic lipophilicity of the neutral piperidine derivatives displays the characteristic response noted for partially fluorinated alkyl groups attached to neutral heteroaryl systems. However, basicity decrease by nearby fluorine substituents affects lipophilicities at neutral pH, so that all partially fluorinated derivatives are of similar or higher lipophilicity than their non-fluorinated parents. Aqueous solubilities were found to correlate inversely with lipophilicity with a significant contribution from crystal packing energies, as indicated by variations in melting point temperatures. All fluorinated derivatives were found to be somewhat more readily oxidized in human liver microsomes, the rates of degradation correlating with increasing lipophilicity. Because the piperidine-2-carboxamide core is chiral, pairs with enantiomeric *N*-alkyl groups are diastereomeric. While little response to such stereoisomerism was observed for basicity or lipophilicity, more pronounced variations were observed for melting point temperatures and oxidative degradation.

Introduction

The incorporation of fluorine into small-molecule leads in chemical discovery, particularly in medicinal chemistry, is gaining prominence. Inclusion of fluorine in drug candidates enables fine-tuning of lipophilicity, basicity, solubility, membrane permeability and metabolic stability.[1] The perceived benefits have led to the development of an ever increasing collection of new reagents, building blocks, and synthetic methods,[2] which allow medicinal chemists to explore the full potential of fluorine in campaigns of lead candidate optimizations.

The replacement of hydrogen by fluorine has been found in general to result in a slight increase in compound lipophilicity.[3] However, there are distinct exceptions, particularly when fluorine is incorporated into aliphatic moieties.[3,4] Systematic studies on lipophilicity-lowering effects by partially fluorinated methyl groups in aliphatic units[5] resulted in a simple C–F bond vector analysis scheme by which local polarity effects and thus modulation of lipophilicity can be satisfactorily predicted for diverse partial fluorination patterns.[6]

In comparisons of conformational or topological isomers with equal numbers of fluorine atoms the differences in local polarity as a result of different C–F bond vector arrangements can be translated more or less directly to changes in molecular lipophilicity since essentially no volume changes are involved. Thus, two fluorine ligands in a *gauche*-vicinal substitution pattern give rise to a substantially larger local dipole moment than two fluorine atoms in a geminal arrangement; hence, *vic*-difluoro alkyl groups exhibit a significantly lower lipophilicity (by $\Delta \log P \sim 0.2$–0.4) than the same alkyl group with a *gem*-difluoro unit.[7] This finding has been used to suggest a 'liponeutral' homologation concept where a small alkyl group with a *gem*-difluoro group can be expanded to its homologous congener without increasing lipophilicity by exchanging the *gem*-difluoro by a *vic*-difluoro substitution pattern.[7]

By contrast, if the numbers of fluorine atoms differ between compared analogues, lipophilicity effects due to changes in molecular volume for each additional fluorine atom have to be accounted for. The series of methyl groups with increasing fluorination provides a prototypic example.[5] Monofluoro- and trifluoromethyl groups exhibit similar local dipole moments; however, the latter has two more fluorines, hence occupies a larger molecular volume. Accordingly, the lipophilicity-lowering effect of a monofluoromethyl group is more substantial than that of its trifluoro counterpart. Furthermore, the difluoromethyl group has a somewhat larger local dipole moment

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than its monofluoromethyl congener. However, the lipophilicity lowering by polarity is just about compensated by the effect due to the volume increase by one additional H/F exchange. This then leads to the characteristic lipophilicity pattern of $CH_3 \gg CH_2F \leq CHF_2 < CF_3$ for small alkyl groups with successive introduction of fluorine at their terminal methyl units.[5–7] Likewise, the substantial lipophilicity-lowering effect of a *vic*-difluoro-substitution pattern suggested the exploration of a *bis*-vicinal trifluoro-substitution pattern which, in the energetically preferred *gauche–gauche* conformation of the three vicinal C–F bonds, would give rise to a substantially increased local dipole moment. However, compared with the *vic*-difluoro case, the additional fluorine ligand does not contribute to a further lipophilicity lowering due to the compensating effect of the volume increase.[7]

Fluorine is also known for its strong modulation of amine basicity. For relatively simple acyclic alkylamines, the basicity-lowering effect is exponentially attenuated with increasing topological distance between fluorine and the basic center.[1c,8] Interestingly, for several fluorine atoms at the same position, such as in a terminal CF_3 group the basicity lowering effect per fluorine atom appears to be additive. For simple fluorinated alkyl groups, the effects largely represent conformational averages, whereas in conformationally restricted cases, particularly in cyclic systems with defined orientation of a C–F bond relative to the basic center, a significant conformational dependence has been well documented.[1c,9] More complex fluorination patterns in *N*-alkyl groups and their influence on lipophilicity and amine basicity have, to the best of our knowledge, not been studied systematically. *N*-alkyl-substituted piperidines with partial fluorination in the exocyclic alkyl group appeared to be of particular interest in order to examine the combined effects of fluorine atoms in various positions and configurations relative to the *N*-alkyl group on both basicity and lipophilicity. *N*-alkyl-substituted piperidines are recurrent structural motifs in medicinal chemistry and encountered in many natural products. A recent survey in Thomson Reuters Integrity^{SM}[10] revealed 218 *N*-propyl and 217 *N*-butyl substituted piperidine-containing drugs on the market or in early biological testing. In addition, there are 30 *N*-propylpiperidines and nine *N*-butylpiperidines which contain fluorine in their *N*-alkyl chains with terminal trifluoromethyl groups being most common.

Herein, we present the results from our study of the effects of such partially fluorinated alkyl chains on pharmacologically relevant properties of piperidines (Figure 1). For our studies we have chosen the non-fluorinated drugs ropivacaine (**1**)[11a] and levobupivacaine (**2**)[11b] both introduced in the market as local anesthetics. They contain an *N*-2,6-dimethylphenyl-substituted carboxamide unit α to the piperidine nitrogen atom with (*S*)-configuration. The bulky substituent may be expected to constrain conformational flexibility of the *N*-alkyl group. Furthermore, the study of the various configurational isomers of the parent (chiral) piperidine allows us to examine the interesting additional feature of epimeric fluorination patterns with intrinsically different physicochemical properties.

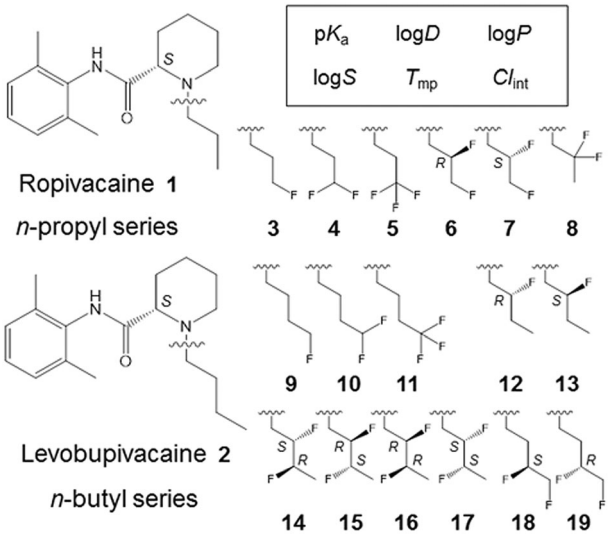
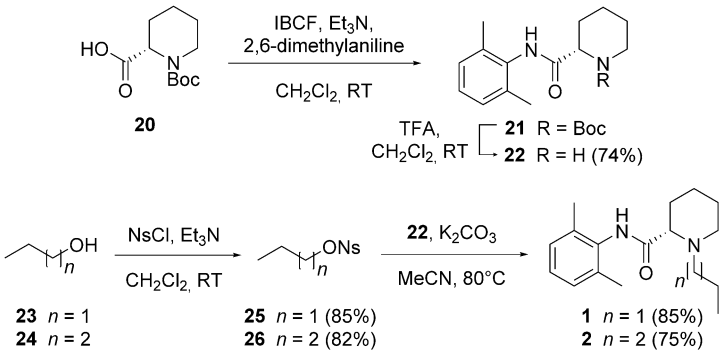


Figure 1. Fluorinated analogues of local anesthetics **1** and **2**.

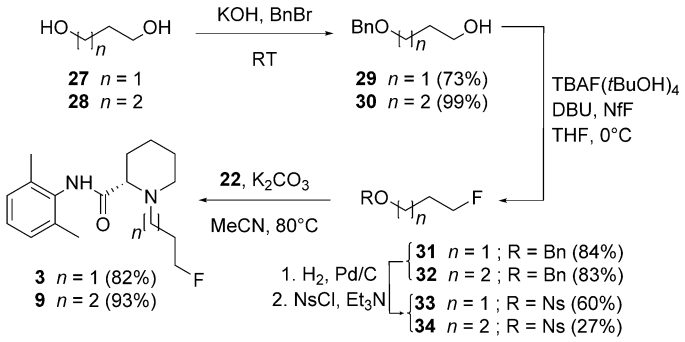
Synthesis

Most of the targeted compounds were obtained by *N*-alkylation of the unprotected (*S*)-piperidine-2-carboxamide **22** (Scheme 1) with the required partially fluorinated alkyl nosylates (4-nitrobenzenesulfonates). Carboxamide **22** was obtained in good overall yield starting from commercially available *N*-Boc-protected (*S*)-enantiopure pipecolic acid (**20**), conversion into **21** via its mixed anhydride, generated from isobutyl chloroformate (IBCF), and treatment with 2,6-dimethylaniline, and subsequent deprotection of **21** with trifluoroacetic acid (TFA). Ropivacaine (**1**) and levobupivacaine (**2**) were obtained by treating carboxamide **22** with nosylated 1-propanol and 1-butanol, respectively, under basic conditions in boiling acetonitrile.[12]

Monofluorides **3** and **9** were synthesized following in parallel a similar synthetic route using propane-1,3-diol (**27**) and



Scheme 1. Synthesis of the *N*-unprotected (*S*)-piperidine-2-carboxamide derivative **22**, the key intermediate for most of the targeted compounds; synthesis of ropivacaine (**1**) and levobupivacaine (**2**).



Scheme 2. Synthesis of terminal monofluorides **3** and **9** by deoxyfluorination of monoprotected diols **29** and **30**.

butane-1,4-diol (**28**) as starting materials (Scheme 2). The diols were allowed to react with sodium hydroxide and benzyl bromide to generate the respective benzyl ethers **29** and **30** in good to excellent yields.[13] Following the procedure reported by Yin et al.[14] both alcohols were then treated with a mixture of DBU, nonaflyl fluoride and *tert*-butyl alcohol-complexed TBAF[15] at 0 °C to form terminal monofluorides **31** and **32** in good yields. Cleavage of the benzyl ether via hydrogenolysis and nosylation of the alcohols formed with 4-nosyl chloride gave fluorides **33** and **34**, which were then coupled to carboxamide **22** to yield *N*-alkylfluoro piperidines **3** and **9** in good yields.

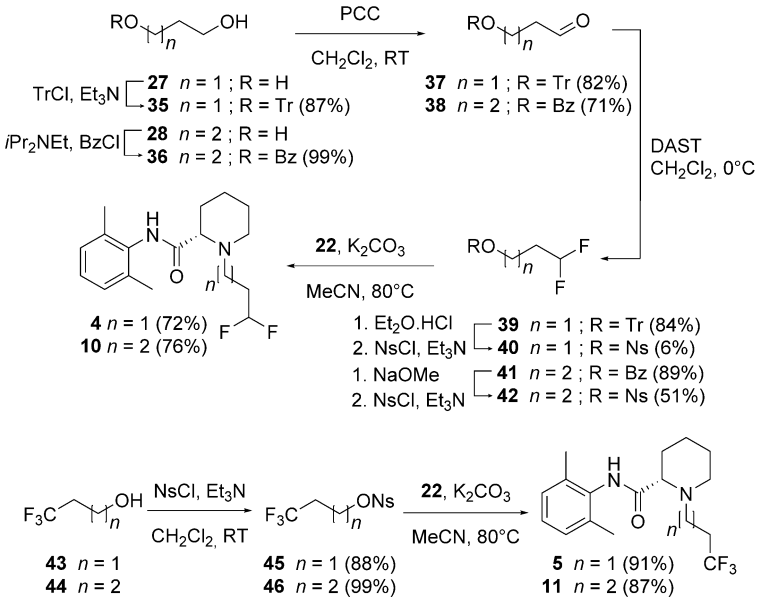
The synthesis of both terminal geminal difluorides **4** and **10** commenced with propane-1,3-diol (**27**) and butane-1,4-diol (**28**). A different protecting group had to be chosen as a consequence of incompatibility of the benzyl ether group with diethylaminosulfur trifluoride (DAST). For diol **28** a benzoyl protecting group proved to be stable under the conditions needed for fluorination, while for diol **27** only triphenylmethyl seemed to tolerate DAST. After protection[16,17] the alcohols were oxidized to aldehydes **37** and **38**[18] with pyridinium chlorochromate (PCC) (Scheme 3).

With the tailor-made protecting groups in place the aldehydes could be converted into their respective geminal difluorides **39** and **41** in good yields by treatment with two equivalents of DAST at 0 °C. While deprotection and nosylation of geminal difluoride **41** gave the desired nosylate **42** in acceptable yields, conversion of the difluoride **39** proved to be problematic due to the volatile nature of the intermediate 3,3-difluoropropanol. Coupling of the nosylates with carboxamide **22** gave terminal difluorides **4** and **10** in good yields.

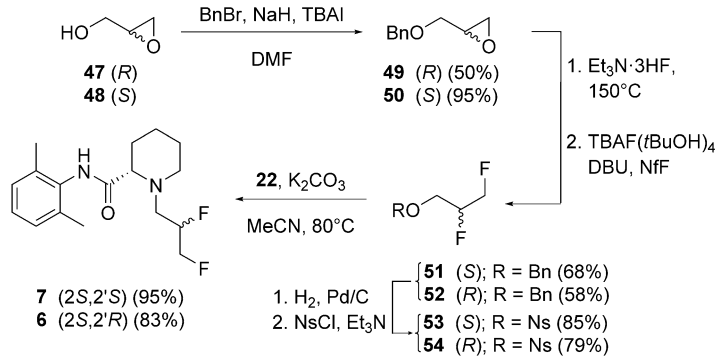
The trifluoro substituted ropivacaine **5** and levobupivacaine derivative **11** were obtained from commercially available 3,3,3-trifluoropropan-1-ol (**43**) and 3,3,3-trifluorobutan-1-ol (**44**) in very good yields over two steps (Scheme 3).

Terminal vicinal difluorides **6** and **7** were synthesized starting from (*R*)-glycidol **47** and its enantiomer **48**, respectively. Following benzyl protection with benzyl bromide and sodium hydride[19] the epoxide was opened by treatment with $Et_3N{\cdot}3HF$ at 150 °C to give regioisomeric mixtures of fluorohydrins, which were converted in good yields to vicinal difluorides **51** and **52** (Scheme 4). Hydrogenolysis of the benzyl ether and nosylation of the primary alcohols gave nosylated difluorides **53** and **54**, which could be readily coupled with carboxamide **22** to produce the targeted difluorides **6** and **7** in high yields.

For the synthesis of the *vic*-difluoro *n*-butyl analogues **18** and **19**, a different route had to be followed since the required chiral epoxides were not commercially available. Following the three-step asymmetric synthesis described by Rapoport and co-workers.[20] the benzylated epoxides **55** and **56** could be prepared in good overall yields from (*R*)- and (*S*)-aspartic acid,

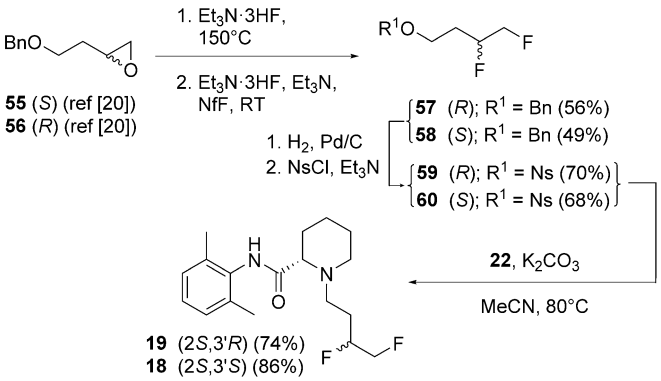


Scheme 3. Synthesis of terminal geminal difluorides **4** and **10**, and trifluoro derivatives **5** and **11**.



Scheme 4. Synthesis of terminal vicinal difluorides **6** and **7** starting from commercially available (*R*)- and (*S*)-glycidol, respectively.

respectively. The epoxides then underwent an analogous epoxide opening/deoxyfluorination sequence to afford terminal vicinal difluorides **57** and **58** in acceptable yields. Replacing the benzyl by the nosyl group and coupling with amide **22** yielded the desired difluorides **18** and **19** in good yields (Scheme 5).



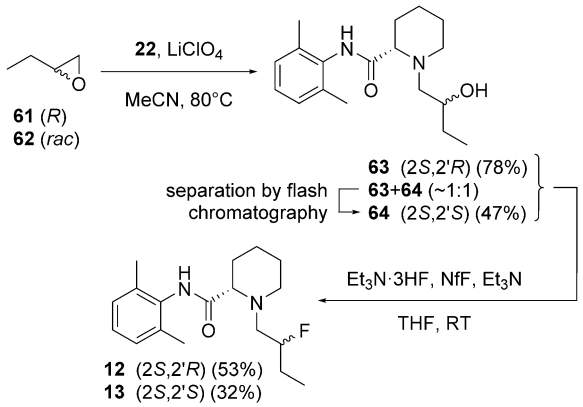
Scheme 5. Synthesis of terminal vicinal difluorides **18** and **19** starting from chiral epoxides **55** and **56**.[20]

Internally monofluorinated compounds **12** and **13** were accessed from commercially available optically active oxirane **61** and its racemate **62**. The epoxides were selectively opened by lithium perchlorate-mediated[21] nucleophilic attack of carboxamide **22** to afford the secondary alcohols. Alcohol **63** was obtained from chiral epoxide **61**, while its epimer **64** was accessed from racemic 2-ethyloxirane **62** after separation of the epimeric mixture by flash column chromatography. Deoxyfluorination of both alcohols with $Et_3N{\cdot}3HF$ and nonaflyl fluoride gave the targeted secondary fluorides **12** and **13** in moderate yields with retention of configuration at the stereogenic center (Scheme 6). The stereochemical assignments for **12** and **13** are based on X-ray crystal structure determinations (Figure 2). A possible explanation for the observed substitution with retention could be a double inversion through the formation of a spiro-aziridinium intermediate upon nosylation of the secondary alcohol with subsequent opening by fluoride.

Geminal difluoride **8** was prepared starting from *N*-Boc protected pipecolic acid **20** (Scheme 7). After benzyl protection of the acid[22] and deprotection of the amine, the piperidine moiety was coupled with chloroacetone under basic conditions to give ketone **67** in good yields. The ketone was then treated with DAST to provide the desired geminal difluoride **68**. Hydrogenolysis of the benzyl ester and subsequent IBCF-mediated amide formation with 2,6-dimethylaniline led to the targeted internal geminal difluoride **8**.

For the synthesis of all isomers of vicinal difluorides (**14**–**17**) no suitable optically active starting material was commercially available. Therefore, we decided to use Sharpless' asymmetric dihydroxylation to access the desired chiral substrates. Ko et al.[23] reported the synthesis of both enantiomers of *erythro* triols **69** and **70** via asymmetric dihydroxylation of (*E*)-(1-(benzyloxy)-but-2-en-4-yl)(*tert*-butyl)diphenylsilane. The procedure of Van-Nieuwenhze and Sharpless[24] was followed to access the other two enantiomers of *threo* triols **71** and **72** from (*Z*)-1-(benzyloxy)but-2-en-4-ol.

Triols **69**–**72** could then be converted in a single step to epoxyfluorides **73**–**76** by reacting them with nonaflyl fluoride



Scheme 6. Three-step preparation of epimeric monofluorobutyl derivatives **12** and **13** starting from commercially available (*R*)-ethyloxirane **61** and racemic ethyloxirane **62**, respectively.

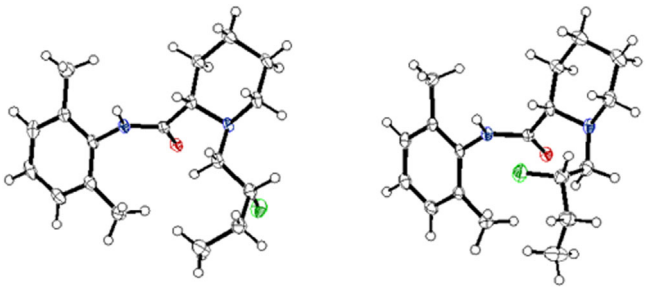
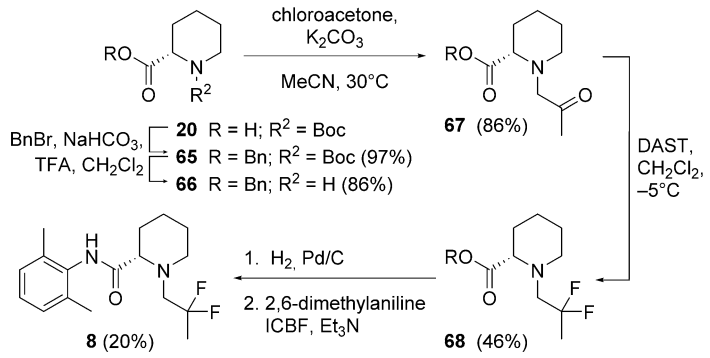
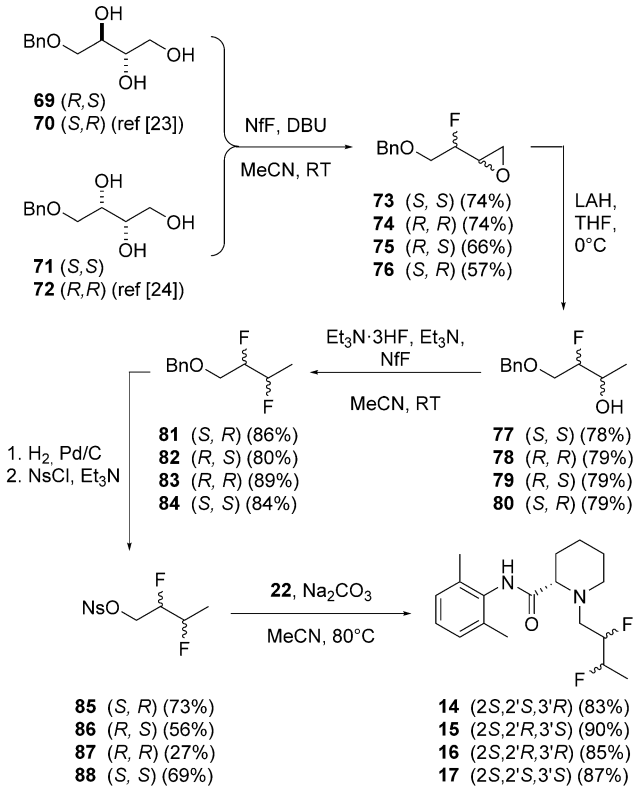


Figure 2. ORTEP plots of the crystal structures of the epimeric monofluorobutyl derivatives **12** (left) and **13** (right) by X-ray diffraction documenting, respectively, (*R*)- and (*S*)-configuration for the 2-fluorobutyl group (see the Supporting Information for experimental details).



Scheme 7. Synthesis of internal geminal difluoride **8**.

and DBU in acetonitrile at room temperature (Scheme 8). Selective epoxide opening from the less hindered primary position with $LiAlH_4$ yielded fluorohydrins **77**–**80** in good yields, followed by deoxyfluorination of the secondary alcohol to afford vicinal difluorides **81**–**84** in excellent yields. Hydrogenolytic deprotection followed by nosylation of the primary alcohol provided nosylates **85**–**88**, which were coupled with carboxamide **22** under basic conditions to afford the targeted internal vicinal difluorides **14**–**17** in good yields.



Scheme 8. Synthesis of diastereomeric *erythro* and *threo vic*-difluoride derivatives **14**–**17** starting from monoprotected *erythro* and *threo* butane triols **69**–**72**.

Results and Discussion

All experimental results are compiled together with structural formulae for easy identification (Figure 3).

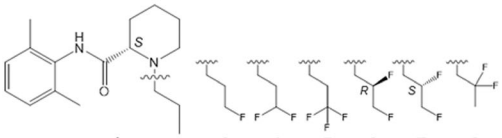
Amine basicity

Both parent compounds **1** and **2** are α-aminocarboxamides and thus exhibit typical moderate basicity,[8] decreased by more than two pK_a units compared to unsubstituted *N*-alkyl piperidines, such as *N*-propyl or *N*-butyl piperidine ($pK_a = 10.5$).[25] Successive introduction of fluorine at the terminal position of the *n*-propyl unit in **1** results in a systematic basicity lowering of $\Delta pK_a = -0.7$, except for the first fluorine substituent for which the pK_a lowering is slightly more pronounced. This observation may be rationalized by noting that 1-fluoropropane in the gas phase exists in an *endo*–*exo* equilibrium for the fluorine atom[26] (Figure 4) with the *endo*-F conformation slightly favored over the more polar *exo*-F arrangement.

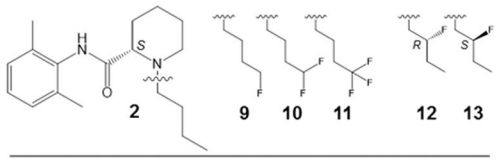
Thus, for **3** in a polar medium the *exo*-fluorine conformation may prevail, in which the terminal fluorine may exert its inductive polarization effectively through an all-*trans* backbone. The second and third fluorine atoms then take the remaining *gauche* positions for which the inductive transmission is slightly reduced and more typical for a fluorine ligand at a γ-alkyl position.[8] A similar, albeit reduced pattern is observed for the stepwise introduction of fluorine at the terminal position of the *n*-butyl group in **2**. The typical basicity reduction for a δ-alkyl position ($\Delta pK_a = -0.3$[8]) is seen for the second and third fluorine substituent, whereas the basicity reduction is slightly more pronounced for the first, which may again indicate a dominant *exo*-arrangement of the first fluorine ligand.

Interestingly, the basicity modulation for *vic*-difluoro derivatives appears to be largely additive. Thus, the total pK_a shifts for the derivatives **18** and **19** correspond to the sum of a terminal fluorine in a δ-*exo* position ($\Delta pK_a = -0.5$) and a γ-*endo* fluorine ($\Delta pK_a \sim -0.7$) with very little dependence on the chirality at C_γ. Likewise, for the *vic*-difluoro substituted *N*-propyl derivatives **6** and **7**, the pronounced basicity reductions result from essentially the cumulative contributions of the γ-*exo* fluorine ($\Delta pK_a = -0.9$) and the fluorine atom in β-*endo* position ($\Delta pK_a = -1.6$ and -1.7, respectively), again with remarkably little response to the chirality at C_β. The ΔpK_a effect thus derived for a β-fluorine substituent corresponds nicely to the value reported earlier in simple unsubstituted alkylamines[8] and also accounts for the substantial basicity-lowering effect observed for the *gem*-difluoro derivative **8** ($\Delta pK_a = 2 \times -1.7$).

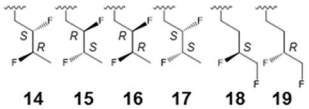
For the two epimeric *n*-butyl derivatives **12** and **13** with a single fluorine substituent in β-position to the piperidine *N*-atom the basicity-lowering effects are similar, albeit slightly reduced. For the four epimeric *vic*-difluoro derivatives **14**–**17**, we note a slightly more pronounced response of basicity modulation to stereochemical differences. While for the two *threo*-isomers **16** and **17**, a *trans*-backbone arrangement is expected, the two *erythro*-isomers are likely to adopt *gauche*-backbone



	1		3	4	5	6	7	8
pK_a	8.2		7.3	6.6	5.9	5.7	5.6	4.8
		ΔpK_a	−0.9	−1.6	−2.3	−2.5	−2.6	−3.4
log$D^{pH=7.4}$	2.1		2.0	2.5	3.0	2.3	2.3	3.0
log$P$	2.9		2.3	2.5	3.0	2.3	2.3	3.0
		Δlog$P$	−0.6	−0.4	0.1	−0.6	−0.6	0.1
log$S^{pH=6.5}$	1.9		2.6	2.1	1.3	2.0	2.8	1.2
T_{mp}[K]	414		408	417	447	433	402	445
Cl_{int}	7 ±7		20 ±11	69 ±7	95 ±12	*n.d.*	*n.d.*	*n.d.*



	2		9	10	11	12	13
pK_a	8.2		7.7	7.4	7.1	6.7	6.6
		ΔpK_a	−0.5	−0.8	−1.1	−1.5	−1.6
log$D^{pH=7.4}$	2.6		*n.d.*	2.5	3.0	3.1	2.9
log$P$	3.4		*n.d.*	2.8	3.2	3.1	2.9
		Δlog$P$	*n.d.*	−0.6	−0.2	−0.3	−0.5
log$S^{pH=6.5}$	3.6		*n.d.*	3.4	2.4	2.0	2.0
T_{mp}[K]	404		388	374	405	377	391
Cl_{int}	26 ±3		*n.d.*	35 ±6	95 ±3	72 ±5	94 ±5



	14	15	16	17	18	19
pK_a	5.5	5.7	5.8	5.6	7.0	6.9
ΔpK_a	−2.7	−2.5	−2.4	−2.6	−1.2	-1.3
log$D^{pH=7.4}$	2.6	2.6	2.7	2.7	*n.d.*	*n.d.*
log$P$	2.6	2.6	2.7	2.7	*n.d.*	*n.d.*
Δlog$P$	−0.8	−0.8	−0.7	−0.7	*n.d.*	*n.d.*
log$S^{pH=6.5}$	2.3	2.5	2.2	2.6	*n.d.*	*n.d.*
T_{mp}[K]	384	415	418	389	401	384
Cl_{int}	48 ±12	36 ±6	75 ±4	85 ±6	*n.d.*	*n.d.*

Figure 3. Summary of fluorine substitution patterns and measured properties for *N*-propylpiperidine-2-carboxamide derivatives **1**, **3**–**8**, and *N*-butylpiperidine-2-carboxamide derivatives **2**, **9**–**19**; the intrinsic lipophilicity (log*P*) of the neutral piperidine derivatives is calculated as $\log P = \log D + \log_{10}(1 + 10^{(pK_a - 7.4)})$; log*S* is the logarithm of the thermodynamic molar solubility ($\mu mol\,L^{-1}$) in 50 mM phosphate buffer at the indicated pH and 22.5 ± 1 °C; for compounds **1**, **3**–**8**, **12**–**14**, log*S* was identical at both pH 6.5 and 10.0; the log*S* values for **15**–**17** were determined at pH 10.0 only; the melting point temperatures (T_{mp}) are given in K and represent average values for temperature ranges given in the Experimental Section; Cl_{int} denotes the pseudo-first-order rate constant of intrinsic clearance ($min^{-1}\,[mg/\mu L_{protein}]^{-1}$), measured in human liver microsomes; see the Experimental Section for further experimental details.

conformations.[27] The latter may place the γ-fluorine substituent into a formal *exo*-position, i.e., antiparallel to the CCC backbone connecting to the piperidine N atom so that a maximum inductive effect can be expected. This may explain the substantial basicity downshift for isomer **14**. Furthermore, we note that for both *threo* and *erythro* isomers, those with an (*S*)-configured C_β center exhibit a slightly larger basicity downshift than their (*R*)-configured counterparts ($\Delta\Delta pK_a \sim 0.2$). However, these basicity differences are remarkably small relative to those observed for monofluorinated piperidine derivatives with a β-fluorine ligand either equatorially or axially oriented,[8] which has been associated with different C–F/N^+–H bond dipole-dipole interactions in the protonated states.[8,28] The small basicity shift differences observed here may thus reflect averages of ΔpK_a effects in complex conformational mixtures. Interestingly, for the singly β-fluorinated epimers **12** and **13** the small basicity shifts are reversed, the (*S*)-configured isomer **13** (corresponding to the isomers **15** and **16** with (*2R*)-configuration) exhibiting a somewhat larger pK_a downshift than its epimeric counterpart **12** (corresponding to the (*2S*)-isomers **14** and **17**).

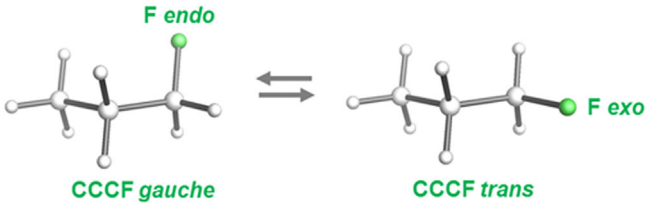


Figure 4. In the gas phase 1-fluoropropane exists as an equilibrium between *gauche* and *trans* conformations, the *gauche* conformation with the fluorine atom in *endo* position being slightly favored;[26] as the *trans* conformation with the fluorine in *exo* position is more polar, it may prevail in polar medium.

Taken together, the basicity shifts for the various monofluoro- and difluoro-substituted derivatives of **1** and **2** display highly consistent patterns of essentially additive contributions of individual, distance-dependent, exponentially attenuated inductive effects for fluorine substituents as reported earlier for simple fluorinated alkylamines.[8] Remarkably, the response to epimeric stereoisomerism is rather modest with variations within 0.1–0.2 pK_a units.

Lipophilicity

Both parent compounds **1** and **2** are weakly basic, so that both are partially protonated in buffered solution at pH 7.4 and exhibit pharmacologically well-accepted lipophilicities of log$D < 3$, with **2** being more lipophilic by 0.5 log*D* units, typical for homology by one saturated carbon unit. Lipophilicity modulation by fluorine keeps the lipophilicity of all derivatives **3**–**19** within a range of ~2.0–3.0. However, since their basicity changes over several pK_a units, intrinsic lipophilicities (log*P*) of the neutral derivatives have to be examined in order to identify characteristic response patterns. For weakly basic compounds log*P* could be determined experimentally in buffered basic solution (e.g., at pH 10) or, alternatively, can be easily calculated from respective log*D* and pK_a values (see Figure 3), assuming that protonated species do not enter the organic phase. Log*D* and log*P* values for all compounds are given in Figure 3.The terminally fluorinated propyl derivatives **3**–**5** display the characteristic lipophilicity pattern of $CH_3 \gg$

$CH_2F \leq CHF_2 \ll CF_3$ as already described for diverse *n*-propyl-substituted benzene and indole series,[5–7] with a substantial lipophilicity drop from the parent compound **1** to the monofluoro derivative, a substantial increase in lipophilicity for the trifluoro derivative, and a lipophilicity of the difluoro analogue close to, albeit slightly higher than that of the monofluoro derivative. A similar if slightly attenuated pattern can also be diagnosed for the homologous series **2**, **9**–**11**, although the lipophilicity of the monofluoro derivative **9** could not be determined due to its instability in aqueous solution above pH 4.5 over prolonged times (this did not affect the pK_a measurements for **9** which were performed in short periods of time). Fluorine displacement by nucleophilic attack of the piperidine nitrogen at the terminal δ-position may be assumed as the initial step of decomposition. This would constitute an intramolecular case, by analogy to the reported fluorine substitution by morpholine in aqueous solution of monofluoro-benzyl derivatives,[29] and would be particularly favored by the formation of a 5-membered ring intermediate. A similar, but less pronounced instability was also observed for the *vic*-difluorobutyl derivatives **18** and **19**. By contrast, the *vic*-difluorobutyl derivatives **14**–**17**, as well as all other partially fluorinated *N*-propyl or *N*-butyl derivatives lacking a single fluorine atom in δ-position, proved to be completely stable. The lipophilicities of **14**–**17** are significantly lower than that of the parent compound **2** and are even slightly more polar than **10** containing a *gem*-difluoro group in full agreement with expectation.[7] Interestingly, very little lipophilicity variation is observed for the four stereoisomers. We note that the two epimeric *threo*-isomers, **16** and **17**, exhibit slightly higher lipophilicity than the corresponding *erythro*-isomers, **14** and **15**. Although the differences in lipophilicity by 0.1 log*P* units are experimentally significant and different carbon backbone conformations may be prevalent for *threo*- and *erythro*-isomers (*trans* backbone versus *gauche* backbone, respectively[27]), we hesitate to provide rationales for these small log*P* differences given potential conformational averaging.

A comparatively strong lipophilicity reduction for *vic*-difluoro substitution is observed for the two epimeric β,γ-difluoro derivatives **6** and **7** in the *N*-propyl series. In these cases, the Δlog*P* shifts are again stronger than that for the *gem*-difluoro derivative **4** and similar to the lipophilicity decrement observed for monofluoro derivative **3**. Remarkably, no response to stereoisomerism is detected, which may point to conformational averaging in solution. By contrast, a small but distinct difference in lipophilicity (Δlog*P* ~ 0.2) is found for the epimeric β-monofluorinated *n*-butyl derivatives **12** and **13** for which significant log*P* depressions are observed.

The geminal *endo*-difluoro derivative **8** is a remarkable case. While its low basicity follows expectations, it exhibits an unusually high lipophilicity in terms of both log*D* and log*P*. Based on previous findings for neutral compounds, the lipophilicity of a geminal *endo*-difluoropropyl derivative would be expected to be equal to or even slightly lower than that of its terminal *gem*-difluoro counterpart **4**.[7] By contrast, however, the lipophilicity of **8** is higher by Δlog*P* = 0.5. We have no explanation for this outlying data point, but speculate that the flanking *N*-arylcarboxamide moiety may induce special conformational properties for the relatively compact 2,2-difluoro *n*-propyl side chain. A detailed comparative structural analysis may shed more light on this compound.

Solubilities

Logarithmic values of micromolar aqueous solubilities (log*S*) are compiled in Figure 3. For a majority of compounds log*S* was determined at both basic (pH 10) and slightly acidic (pH 6.5) conditions (see Experimental Section). Remarkably, solubilities for all these compounds, having pK_a values in the range of 4.8 to 8.2, are essentially identical, thus independent of the degree of piperidine protonation.

The two parent compounds **1** and **2** differ substantially in their solubilities, the more lipophilic **2** being more soluble than **1** by almost two log*S* units. This illustrates that lipophilicity is not the only property determining aqueous solubility; hence, simple correlations of log*S* against log*D* should not be expected. Equally and potentially even more important are crystal packing energies. Because the latter are not available we may use melting point temperatures (T_{mp}) as a rough surrogate for this important parameter.

A qualitatively good correlation of log*S* versus log*D* is observed for the short series of **1** and its terminally fluorinated analogues **3**–**5**, where the most polar compound **3** is also the most soluble. Introduction of additional terminal fluorines results in a systematic increase in lipophilicity and concomitant solubility drop with the most lipophilic compound **5** becoming the least soluble. Interestingly, the lipophilicity of **5**, in terms of both log*D* and log*P*, is similar to the *gem-endo*-difluoro derivative **8**; and both compounds also exhibit very similar low solubility.

The fact that solubility does not in general simply follow lipophilicity is nicely demonstrated by the pair of epimeric monofluoro derivatives **6** and **7** with identical lipophilicity and very similar partial protonation at pH 6.5, but markedly different aqueous solubilities (Δlog*S* ~ 0.8). Compound **6** shows a solubility close to that of the non-fluorinated parent compound **1**, whereas the solubility of the epimeric **7** even surpasses that of the most polar compound (**3**) of this series. Different crystal packing energies may be the origin for this observation as indicated by the melting point temperatures of the two epimers differing by more than 30°.

In the homologous *n*-butyl series with terminal fluorine substitution, we may speculate that for the four compounds **2**, **9**–**11** similar qualitative correlation with lipophilicities may operate. Unfortunately, the solubility of the terminally mono-fluorinated analogue **9** could not be determined due to its instability in aqueous solution for prolonged times (see above). However, the log*S* pattern for the remaining three members indeed follow that of the *n*-propyl analogues.

For the four stereoisomers **14**–**17** with marginally different lipophilicities (Δlog*D* = Δlog*P* ≤ 0.1) solubilities differ within a relatively narrow range of only a factor of 2 (Δlog*S* ≤ 0.3). By contrast to the case of **6** and **7**, the two homologous epimeric *endo* monofluoro-derivatives **12** and **13**, which exhibit small

but significant difference in lipophilicity ($\Delta\log D = \Delta\log P \sim 0.2$), show virtually identical aqueous solubility.

It is instructive to compare the correlations of log*S* against either log*D* or T_{mp} (Figure 5 and Figure 6). Figure 5 shows that the *n*-propyl derivatives (**1**, **3**–**8**) correlate reasonably well with their lipophilicities ($R^2 > 0.65$), and a somewhat weaker correlation ($R^2 > 0.4$) can be diagnosed for the collection of *n*-butyl derivatives (**2**, **10**–**17**). On the other hand, solubilities in the *n*-

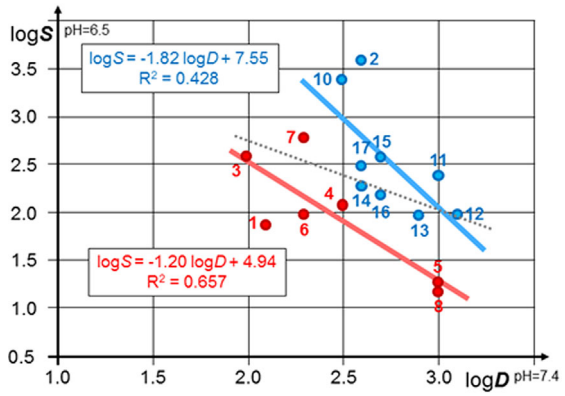


Figure 5. Correlation of $\log S^{pH6.5}$ versus $\log D^{pH7.4}$ for the *N*-propyl series **1**, **3**–**8** (red dots) and *N*-butyl series **2**, **10**–**17** (blue dots). While there is very little correlation for both series together ($R^2 = 0.133$, grey dotted line), the individual series exhibit moderate (blue line) to reasonably good (red line) correlations, parameters being given in blue and red, respectively.

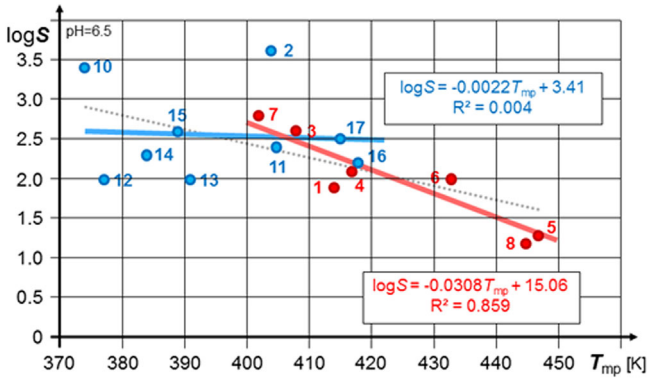


Figure 6. Correlation of $\log S^{pH6.5}$ versus (absolute) melting point temperatures T_{mp} in K. For the *N*-propyl series **1**, **3**–**8** (red dots) and *N*-butyl series **2**, **10**–**17** (blue dots); while the *N*-butyl series shows no correlation ($R^2 \sim 0$, blue line), the *N*-propyl series exhibits a relatively strong correlation (red line). Both sets together then display a moderate correlation ($R^2 = 0.377$, grey dotted line), where the blue scattered dots borrow correlation from the red set. Correlation parameters are given in blue and red, respectively.

propyl series correlate quite strongly with melting point temperature ($R^2 > 0.85$) (Figure 6), whereas no such correlation can be found within the collection of *n*-butyl derivatives ($R^2 \sim 0$). Tentatively we may take these findings to illustrate a higher diversity of crystal packing energies for the conformationally more flexible partially fluorinated *n*-butyl derivatives. On the other hand, it is comforting to note the parallel correlation of solubilities with lipophilicities and melting point temperatures for the series of less flexible *n*-propyl derivatives with more significant contributions of crystal packing energies to solubility properties.

Metabolic stability

Metabolic stabilities of some of the novel partially fluorinated *n*-propyl and *n*-butyl-substituted piperidine-2-carboxamide derivatives were measured in human liver microsomal degradation assays. The intrinsic pseudo-first-order decay rate constants (Cl_{int}) are given in Figure 3. While most Cl_{int} data come with reasonably narrow error limits, some exhibit larger variations due to difficult experimental compound detection and thus have to be considered with due caution. Nevertheless, the overall patterns based on the mean Cl_{int} values remain essentially unaffected.

The Cl_{int} rates correlate approximately with log*D* at neutral pH. Thus, the more lipophilic homologous parent compound **2** is more readily oxidized than its congener **1**, which is metabolically the most stable compound of the whole compound collection. The most polar monofluoropropyl derivative **3** is slightly more rapidly metabolized although the Cl_{int} values for **1** and **3** are rather close with overlapping error limits. While the mode(s) of oxidative degradation have not been determined and more than one mechanism may be operating, it is somewhat sobering that all partially fluorinated derivatives in the *n*-propyl and *n*-butyl series examined in this study are slightly more rapidly metabolized up to approximately one order of magnitude than their respective non-fluorinated parents. On the other hand, and in contrast to the partially fluorinated neutral alkylindole derivatives reported earlier,[7] the current series contains a basic piperidine core. Partial fluorination thus not only results in the characteristic modulation of intrinsic lipophilicity (log*P*), but also in a lowering of basicity, which then keeps the lipophilicity at neutral pH ($\log D^{pH7.4}$) of the partially protonated derivatives at essentially the same or mostly higher values than those of the respective parent compounds. This is nicely borne out by the terminally mono-, di-, and trifluorinated propyl derivatives **3**, **4**, and **5**, which exhibit increasing lipophilicity $\log D^{pH7.4}$ and concomitantly accelerated rates of metabolic degradation. A very similar pattern is also shown by the di- and trifluorinated butyl derivatives **10** and **11**. As a consequence, the most lipophilic trifluoromethyl derivatives **5** and **11** in these two short series are metabolically the least stable compounds, which contrasts the general notion of a metabolic blocking effect by CF_3 groups.[1a,30] Interestingly, a reasonably good correlation ($R^2 > 0.68$) is obtained between Cl_{int} and log*D* of all compounds examined (Figure 7), which is consistent with the notion that increased compound lipophilicity may concur with enhanced metabolic oxidation.[31]

Conclusions

A series of partially fluorinated *N*-propyl and *N*-butyl analogues of ropivacaine and levobupivacaine were synthesized in order to study the modulation of pharmacologically relevant properties by incorporation of various fluorination patterns into the

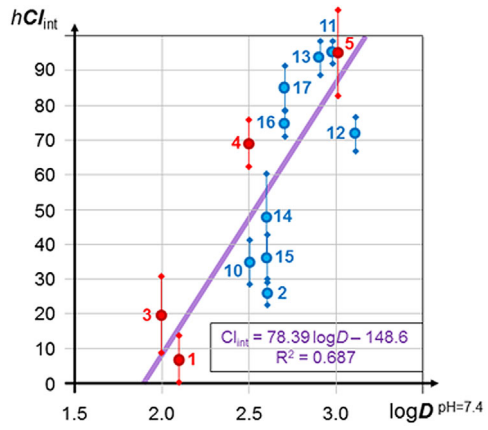


Figure 7. Correlation of intrinsic pseudo-first-order decay rate constants from human microsomal assays (Cl_{int}, data in Figure 3) with lipophilicities $\log D^{pH\,7.4}$ for compounds of the *N*-propyl- (red dots) and *N*-butyl (blue dots) series (data in Figure 3). Both series together exhibit a reasonable correlation (violet line).

linear alkyl groups. For all derivatives the pK_a downshifts due to fluorine substituents at different positions in the alkyl units are found to be largely additive and predictable by a simple exponential attenuation as a function of topological distance between a fluorine substituent and the basic nitrogen center. Specific fluorination patterns modulate the intrinsic lipophilicity (log*P*) of the neutral piperidine derivatives in a similar way as previously observed for neutral alkylindole derivatives. However, the concurrent decrease in amine basicity compensates for log*P* lowering and results in somewhat increased lipophilicities at neutral pH ($\log D^{pH\,7.4}$) due to reduced partial protonation of the basic nitrogen center. This is seen to affect both metabolic stability and solubility. The oxidative degradation of the measured derivatives in microsomal assays remained within one order of magnitude compared with the non-fluorinated parent compounds and correlated reasonably well with the increase of lipophilicity within a range of one log*D* unit. Variation of aqueous solubility could also be partially rationalized by variation of lipophilicity (log*D*). However, in certain cases clear evidence for the importance of crystal lattice energies has been obtained. Essentially all partially fluorinated *N*-propyl and *N*-butyl derivatives proved to be chemically stable in buffered aqueous solutions over prolonged periods of time, except derivatives having a single fluorine substituent in δ-position to the basic amine center. While a second or third fluorine substituent in δ-position fully restores chemical stability, a second fluorine in γ-position to form a *vic*-difluoro substituted derivative, reduces but not completely eliminates chemical reactivity at the δ-position.

Taken together, this study adds to our knowledge of partially fluorinated alkyl groups when attached to the nitrogen atom of a moderately basic amine and thus complements previous studies of such groups attached to neutral heteroaryl systems. While a number of earlier observations about changes of physicochemical properties have been confirmed some property modulations are unique and can be traced to the strong reduction of amine basicity by fluorine substituents in the closer vicinity of the basic center. Likewise, the influence of the adjacent *N*-aryl carboxamide is found to have surprisingly little influence on the effects exerted by various fluorination patterns, except for the singular case of the geminal *endo*-difluoropropyl derivative which turns out to be unusually lipophilic. Further structural studies are underway to investigate this case.

Experimental Section

Materials and analytical methods: All non-aqueous reactions were carried out using oven-dried (90 °C) glassware under a positive pressure of dry nitrogen unless otherwise noted. Tetrahydrofuran, diethyl ether, toluene, and methylene chloride were purified by distillation and dried by passage over activated alumina under an argon atmosphere (H_2O content <30 ppm, Karl–Fischer titration). Dioxane was distilled from calcium hydride under an inert atmosphere. Triethylamine was distilled from KOH under an atmosphere of dry nitrogen. All other commercially available reagents were used without further purification. Except if indicated otherwise, reactions were magnetically stirred and monitored by thin-layer chromatography using Merck Silica Gel 60 F_{254} or Merck Aluminum oxide 60 F_{254} plates and visualized by fluorescence quenching under UV light. In addition, TLC plates were stained using ceric ammonium molybdate or potassium permanganate stain. Chromatographic purification of products (flash chromatography) was performed on E. Merck Silica Gel 60 (230–400 mesh) using a forced flow of eluent at 0.3–0.5 bar. Concentration under reduced pressure was performed by rotary evaporation at 40 °C at the appropriate pressure, unless otherwise stated. Purified compounds were further dried for 12–72 h under high vacuum (0.01–0.05 Torr). Yields refer to chromatographically purified and spectroscopically characterized compounds, unless otherwise stated. For property measurements samples were further purified if needed by HPLC on Reprosil Chiral-NR columns (50 mm × 250 mm, particle size 8 μm) under isocratic conditions with solvent mixtures of *n*-heptane and ethanol in various ratios as indicated individually to purity of ≥ 99.5 %.

Melting point temperatures (T_{mp}) were measured on a Büchi 510 apparatus. All melting points were measured in open capillaries and are uncorrected.

Optical rotations ($[\alpha]_D$) were measured at 25 ± 1 °C on the sodium D wavelength using a Jasco P-2000 Polarimeter equipped with a 10 cm, 1 mL cell, at concentrations of 1–10 mg mL^{-1}, and calculated for concentrations of g per 100 mL (indicated as $c = 1.0$ in *Synthetic procedures* below); specific optical rotations are given in units of deg dm^{-1} (g mL^{-1})$^{-1}$.

NMR, IR, and MS: Proton nuclear magnetic resonance (^{1}H NMR) spectra, carbon nuclear magnetic resonance (^{13}C NMR) spectra, and fluorine nuclear magnetic resonance (^{19}F NMR) spectra were recorded on Bruker AV400 (400 MHz) spectrometer. Chemical shifts (δ) are reported in ppm with the solvent resonance as the internal standard relative to chloroform (δ 7.26) for 1 H, and chloroform (δ 77.16) for ^{13}C. ^{19}F NMR spectra are referenced relative to $CFCl_3$ in $CDCl_3$. Coupling constants (*J*) are given in units of hertz (Hz). All ^{13}C spectra were measured with complete proton decoupling, unlike ^{19}F NMR spectra. Multiplicities are abbreviated by s (singlet), bs (broad singlet), d (doublet), dd (doublet of doublet), t (triplet), dt (doublet of triplet), td (triplet of doublet), tt (triplet of triplet), q (quartet), qd (quartet of doublet), p (quintet), h (sextet), and m (multiplet). IR spectra were recorded on a PerkinElmer Spectrum RXI FT-IR spectrophotometer. Absorption band positions are given

in wave numbers (cm^{-1}). Mass spectra were recorded by the MS service at ETH Zürich, using EI-MS (*m/z*) on a VG-TRIBRID spectrometer, and MALDI-MS (*m/z*) on a IonSpec Ultima Fourier Transform Mass Spectrometer.

Determination of ionization constants (pK_a): Ionization constants are determined at 23 ± 1 °C by spectrophotometry using a ProfilerS-GA SIRIUS instrument in buffered water solution at an ionic strength of 150 mM. To this end the UV spectrum of a compound is measured at different pH values. The solution of the sample is injected at constant flow rate into a flowing pH gradient. Changes in UV absorbance are monitored as a function of the pH gradient. The pK_a values are found and determined where the rate of change of absorbance is at a maximum. The pH gradient is established by proportionally mixing two flowing buffer solutions. The buffer solutions contain mixtures of weak acids and bases that are UV-spectroscopically transparent above 240 nm. It is necessary to calibrate the gradient in order to know exactly the pH at any given time. This is achieved by introducing standard compounds with known pK_a values.

Determination of lipophilicity ($logD^{pH\,7.4}$): Measurements of log*D* start with the accurate coating of the hydrophobic layer (0.45 μm PVDF membranes), which is fixed on the bottom of each DIFI© tube. The coated membranes are then connected to a 96-well plate prefilled with exactly 150 μL of an aqueous buffer solution (25 mM PO, pH 7.4) containing the compound of interest at a start concentration of at least 85 μM. To expand the measurement range of $-0.5 \le \log D \le 4$, it is necessary to carry out the procedure at two different octanol/water ratios, one with an excess of octanol for hydrophilic compounds ($\log D < 1$) and one with a low volume of octanol for the lipophilic compounds ($\log D > 1$). Therefore, part of the DIFI© tubes are filled with 15 μL 1-octanol and another part with 1 μL 1-octanol. The resulting sandwich ensures that the membrane is completely immersed in the buffer solution. The plate is then sealed and shaken for 12 h at room temperature (23 °C). During this time the substance is distributed between the layer, the octanol, and the buffer solution. After reaching equilibrium distribution the DIFI© tubes are disassembled from the top of the 96-well plate, and the resultant sample concentration in the aqueous phase is determined by LC–MS.

Determination of solubility ($logS^{pH\,6.5}$, $logS^{pH\,10.0}$): For each compound, a sample of ~2 mg was added to 150 μL of a 50 mM aqueous phosphate buffer at pH 6.5 and transferred to a standard 96-well plate at room temperature (22.5 ± 1 °C). For determination of log*S* at pH 10.0, compound suspensions were treated with a concentrated NaOH solution. The 96-well plate was placed on a plate shaker which agitated the suspensions overnight. At the next day the samples were filtered with a micronic filter plate (MSGVN2250) to separate the solid material from the solution. After confirming unchanged pH of the solutions by way of micro-pH-meter measurements, the solution concentrations were determined by calibrated HPLC. The calibrations were obtained by HPLC analysis of different concentrations of each compound in DMSO.

Determination of metabolic stability (Cl_{int}): Microsomal incubations were carried out in 96-deep-well plates with a final incubation volume of 600 μL. Each incubation contained 2 μM of test compound, 0.5 mg mL^{-1} human liver microsomes and NADPH regenerating system, containing potassium phosphate buffer (50 mM, pH 7.4), $MgCl_2$ (10 mM), EDTA (1 mM), $NADP^+$ (2 mM), glucose-6-phosphate·$2H_2O$ (20 mM), glucose-6-phosphate dehydrogenase (4 units/mL). Test compounds were incubated for up to 45 min at 37 °C under vortexing at 800 rpm. Aliquots of 50 μL were removed after 1, 3, 6, 9, 15, 25, 35, and 45 min and quenched in 150 μL acetonitrile containing internal standard. Samples are then cooled and centrifuged before analysis by high-performance liquid chromatography (HPLC) coupled with tandem-mass spectrometry (LC–MS/MS). The system consisted of a *Shimadzu* binary gradient HPLC system, a Waters XTerra® MS C18 column (1 mm × 50 mm) and a Sciex API 2000 mass spectrometer. A two-component mobile phase, pumped at 0.15 mL min^{-1}, contained the following solvents: solvent A (1% aqueous formic acid and MeOH 80:20) and solvent B (MeOH). An initial isocratic step of 0.5 min solvent A was followed by a gradient of 0 to 80% solvent B within 1 min. Detection was performed in positive mode. Log peak area ratios (test compound peak area/internal standard peak area) were plotted against incubation time, and a linear fit was made with an emphasis on the initial rate of compound disappearance. The slope of the fit is used to estimate a pseudo-first-order rate constant of intrinsic clearance, Cl_{int} in units of min^{-1}/(mg μL^{-1} protein concentration) with a 95%-confidence interval from the measurements at eight successive time points.

Synthetic procedures

(*S*)-*N*-(2,6-Dimethylphenyl)-1-propylpiperidine-2-carboxamide (Ropivacaine) (1): To a stirring solution of propyl 4-nitrobenzenesulfonate (**25**) (0.28 g, 1.1 mmol) in 1.5 mL acetonitrile was added a solution of (*S*)-*N*-(2,6-dimethylphenyl)piperidine-2-carboxamide (**25**) (0.28 g, 1.1 mmol, 1.0 equiv) in 1.5 mL acetonitrile and K_2CO_3 (0.34 g, 2.5 mmol, 2.2 equiv). The reaction mixture was brought to 80 °C and stirred for 5.5 h, then allowed to cool to room temperature. The reaction was quenched with saturated $NaHCO_3$ (20 mL) and the mixture extracted with EtOAc (3 × 20 mL). The organic layer was washed with brine (50 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (4:1 to 2:1 hexane/EtOAc) to give Ropivacaine (**1**) (0.29 g, 1.1 mmol, 94% yield) as a white solid. 97.0% purity by analytical HPLC; 99.9% purity after preparative HPLC (Reprosil Chiral-NR, heptane/EtOH = 80:20). TLC: $R_f = 0.3$ (2:1 hexane/EtOAc; UV, $KMnO_4$); mp: 139–143 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 8.15 (brs, 1H), 7.13–7.05 (m, 3H), 3.20 (dtd, $J = 11.8$, 3.8, 1.3 Hz, 1H), 2.88 (dd, $J = 10.4$, 3.6 Hz, 1H), 2.79 (ddd, $J = 12.5$, 10.5, 6.1 Hz, 1H), 2.25 (s, 6H), 2.28–2.17 (m, 1H), 2.15–2.08 (m, 1H), 2.05 (td, $J =$ 11.5, 2.8 Hz, 1H), 1.82–1.63 (m, 4H), 1.58–1.46 (m, 2H), 1.34 (d, $J =$ 12.1 Hz, 1H), 0.91 ppm (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta =$ 172.98, 135.34, 133.71, 128.33, 127.06, 68.64, 59.47, 51.65, 30.78, 24.95, 23.56, 20.72, 18.75, 11.63 ppm; IR (neat): $\tilde{\nu} =$ 3170, 2929, 1652, 1531, 1464, 1220, 897, 767 cm^{-1}; HRMS (ESI+) *m/z*: exact mass calculated for $C_{17}H_{27}N_2O$ $[M+H]^+$, 275.2118; found 275.2118; $[\alpha]_D^{25} = -111.0$ ($c = 1.0$, $CHCl_3$).

(*S*)-1-Butyl-*N*-(2,6-dimethylphenyl)piperidine-2-carboxamide (Levobupivacaine) (2): To a stirring solution of (*S*)-*N*-(2,6-dimethylphenyl)piperidine-2-carboxamide (**22**) (0.56 g, 2.4 mmol, 1.2 equiv) and Na_2CO_3 (0.46 g, 4.4 mmol, 2.2 equiv) in 1.5 mL MeCN was added butyl 4-nitrobenzenesulfonate (**26**) (0.52 g, 2.0 mmol, 1.0 equiv) in 2 mL MeCN. The reaction mixture was heated at 80 °C and monitored by TLC. After 19 h the reaction mixture was allowed to cool to room temperature and diluted with EtOAc (50 mL). The mixture was then washed with saturated $NaHCO_3$ (3 × 50 mL). The organic layer was washed with brine (50 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (4:1 to 2:1 hexane/EtOAc) to give the Levobupivacaine (**2**) (0.50 g, 1.7 mmol, 87% yield) as a white solid. 100% purity by analytical HPLC (Lux 5μ Cellulose-2). TLC: $R_f = 0.37$ (7:3 hexane/EtOAc; UV, $KMnO_4$); mp: 130–132 °C; ^{1}H NMR

(400 MHz, $CDCl_3$): $\delta = 8.16$ (brs, 1H), 7.14–6.99 (m, 3H), 3.21 (dtd, $J = 11.7$, 3.9, 1.3 Hz, 1H2), 2.93–2.75 (m, 2H), 2.33–2.22 (m, 1H), 2.25 (m, 6H), 2.17–1.99 (m, 2H), 1.85–1.61 (m, 4H), 1.60–1.45 (m, 2H), 1.43–1.26 (m, 3H), 0.92 ppm (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 173.09$, 135.44, 133.85, 128.45, 127.16, 68.72, 57.70, 51.80, 30.85, 29.92, 25.05, 23.67, 20.82, 18.89, 14.29 ppm; IR (neat): $\tilde{\nu} = 3173$, 2934, 2851, 1648, 1524, 1464, 1225, 765; HRMS (EI+) *m/z*: exact mass calculated for $C_{18}H_{29}N_2O$ $[M+H]^+$, 289.2274; found 289.2278; $[\alpha]_D^{25} = -108.6$ ($c = 1.0$, $CHCl_3$).

(*S*)-*N*-(2,6-Dimethylphenyl)-1-(3-fluoropropyl)piperidine-2-carboxamide (3): To a stirring solution of (*S*)-*N*-(2,6-dimethylphenyl)piperidine-2-carboxamide (**22**) (0.46 g, 2.0 mmol, 1.2 equiv) in 4 mL MeCN was added Na_2CO_3 (0.39 g, 3.7 mmol, 2.2 equiv) and 3-fluoropropyl 4-nitrobenzenesulfonate (**33**) (0.44 g, 1.67 mmol, 1.00 equiv) in 3 mL MeCN, and the reaction mixture was stirred at reflux temperature for 14 h. The reaction mixture was allowed to cool to room temperature and diluted with EtOAc (30 mL). The mixture was extracted with saturated $NaHCO_3$ (3×20 mL) and the organic layer was washed with brine (40 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (2:1 to 1:2 hexane/EtOAc) to give fluoride (**3**) (0.45 g, 1.5 mmol, 93% yield) as a white solid. 96.8% purity by analytical HPLC; 99.6% purity after preparative HPLC (Reprosil Chiral-NR, heptane/EtOH = 80:20). TLC: $R_f = 0.31$ (3:2 hexane/EtOAc; UV, $KMnO_4$); mp: 134–136 °C; ^1H NMR (400 MHz, $CDCl_3$): $\delta =$ 8.06 (s, 1H), 7.13–7.04 (m, 3H), 4.65–4.39 (m, 2H), 3.22–3.14 (m, 1H), 3.06 (ddd, $J = 12.7$, 9.5, 6.9 Hz, 1H), 2.93 (dd, $J = 10.0$, 3.6 Hz, 1H), 2.45–2.36 (m, 1H), 2.25 (s, 6H), 2.17–1.84 (m, 4H), 1.83–1.69 (m, 3H), 1.59–1.47 (m, 1H), 1.43–1.30 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 172.63$, 135.51, 133.76, 128.46, 127.26, 82.20 (d, $J = 165.4$ Hz), 68.68, 53.41 (d, $J = 4.3$ Hz), 51.64, 30.75, 28.45 (d, $J = 19.7$ Hz), 24.89, 23.61, 18.89 ppm (d, $J = 1.0$ Hz); ^{19}F NMR (377 MHz, $CDCl_3$, decoupled): $\delta = -219.66$ ppm; ^{19}F NMR (377 MHz, $CDCl_3$, not decoupled): $\delta = -219.66$ ppm (tt, $J = 47.1$, 26.6 Hz); IR (neat): $\tilde{\nu} = 3177$, 3024, 2929, 1651, 1531, 1473, 1435, 1316, 1263, 1225, 1043, 961, 909, 770, 727 cm^{-1}; HRMS (ESI+) *m/z*: exact mass calculated for $C_{17}H_{26}FN_2O$ $[M+H]^+$, 293.2024; found 293.2030; $[\alpha]_D^{25} = -100.7$ ($c = 1.0$, $CHCl_3$).

(*S*)-1-(3,3-Difluoropropyl)-*N*-(2,6-dimethylphenyl)piperidine-2-carboxamide (4): To a stirring solution of (*S*)-*N*-(2,6-dimethylphenyl)piperidine-2-carboxamide (**22**) (0.22 g, 0.8 mmol, 1.0 equiv) in 1.5 mL MeCN was added potassium carbonate (0.24 g, 1.7 mmol, 2.2 equiv) and 3,3-difluoropropyl 4-nitrobenzenesulfonate (**40**) (0.22 g, 0.8 mmol, 1.0 equiv) dissolved in 2 mL MeCN. The reaction mixture was heated at 80 °C and stirred for 12 h, then allowed to cool to room temperature. The reaction was quenched with saturated $NaHCO_3$ (20 mL) and the mixture extracted with EtOAc (3× 20 mL) and the collected organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (8:1 to 6:1 hexane/EtOAc) to give difluoride **4** (187 mg, 0.60 mmol, 76% yield) as a white solid. 96.6% purity by analytical HPLC; 100% purity after preparative HPLC (Reprosil Chiral-NR, heptane/EtOH = 80:20). TLC: $R_f = 0.31$ (3:2 hexane/EtOAc; UV, $KMnO_4$); mp: 142–146 °C; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.96$ (s, 1H), 7.12–7.05 (m, 3H), 5.90 (tt, $J = 56.4$, 4.4 Hz, 1H), 3.19–3.13 (m, 1H), 3.07 (ddd, $J = 12.8$, 9.4, 7.1 Hz, 1H), 2.94 (dd, $J = 9.9$, 3.6 Hz, 1H), 2.48 (ddd, $J = 12.8$, 9.1, 4.9 Hz, 1H), 2.24 (s, 6H), 2.22–2.02 (m, 4H), 1.84–1.69 (m, 3H), 1.60–1.47 (m, 1H), 1.44–1.31 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 172.25$, 135.45, 133.63, 128.50, 127.34, 116.32 (t, $J =$ 239.3 Hz), 68.60, 51.58, 50.19, 32.14 (t, $J = 20.9$ Hz), 30.59, 24.76, 23.48, 18.86 ppm; ^{19}F NMR (377 MHz, $CDCl_3$, decoupled): $\delta =$ −116.01 ppm (d, $J = 1.73$ Hz, 2F); ^{19}F NMR (377 MHz, $CDCl_3$, not decoupled): $\delta = -116.01$ ppm (dtd, $J = 56.5$, 17.4, 1.7 Hz, 2F); IR (neat): $\tilde{\nu} = 3175$, 2949, 2857, 1714, 1651, 1533, 1471, 1438, 1398, 1232, 1121, 1108, 1040, 907, 772, 730 cm^{-1}; HRMS (ESI+) *m/z*: exact mass calculated for $C_{17}H_{25}F_2N_2O$ $[M+H]^+$: 311.1929; found: 311.1929; $[\alpha]_D^{25} = -83.9$ ($c = 1.0$, $CHCl_3$).

(*S*)-*N*-(2,6-Dimethylphenyl)-1-(3,3,3-trifluoropropyl)piperidine-2-carboxamide (5): To a stirring solution of (*S*)-*N*-(2,6-dimethylphenyl)piperidine-2-carboxamide (**22**) (0.22 g, 0.95 mmol, 1.1 equiv) in 1.5 mL acetonitrile was added Na_2CO_3 (0.20 g, 1.9 mmol, 2.2 mmol) and 3,3,3-trifluoropropyl 4-nitrobenzenesulfonate (**45**) (0.26 g, 0.87 mmol, 1.0 equiv) in 5 mL acetonitrile. The reaction mixture was stirred at 80 °C for 20 h, then diluted with EtOAc (5 mL) and washed with saturated $NaHCO_3$ (3×20 mL). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (4:1 to 1:1 hexane/EtOAc) to afford trifluoride **5** (0.25 g, 0.75 mmol, 87%) as a white solid. 97.2% purity by analytical HPLC; 100% purity after preparative HPLC (Reprosil Chiral-NR, heptane/EtOH = 90:10). TLC: $R_f = 0.27$ (3:1 hexane/EtOAc; UV, $KMnO_4$); mp: 171–176 °C; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.97$ (s, 1H), 7.16–7.04 (m, 3H), 3.18–3.06 (m, 2H), 2.98 (dd, $J = 9.9$, 3.7 Hz, 1H), 2.61 (ddd, $J =$ 12.9, 9.9, 4.9 Hz, 1H), 2.51–2.28 (m, 2H), 2.24 (s, 6H), 2.22–2.06 (m, 2H), 1.84–1.70 (m, 3H), 1.60–1.48 (m, 1H), 1.45–1.33 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 171.98$, 135.38, 126.56 (q, $J =$ 276.7 Hz), 68.26, 51.53, 49.82 (q, $J = 3.0$ Hz), 32.12 (q, $J = 27.8$ Hz), 24.59, 18.81 ppm; ^{19}F NMR (377 MHz, $CDCl_3$, decoupled): $\delta =$ −64.87 ppm (s, 3F); ^{19}F NMR (377 MHz, $CDCl_3$, not decoupled): $\delta =$ −64.87 ppm (t, $J = 10.6$ Hz, 3F); IR (neat): $\tilde{\nu} = 3264$, 2948, 1655, 1502, 1253, 1143, 1110, 990, 765 cm^{-1}; HRMS (ESI+) *m/z*: exact mass calculated for $C_{17}H_{24}F_3N_2O$ $[M+H]^+$: 323.1835; found: 329.1839; $[\alpha]_D^{25} = -75.9$ ($c = 1.0$, $CHCl_3$).

(*S*)-1-((*R*)-2,3-Difluoropropyl)-*N*-(2,6-dimethylphenyl)piperidine-2-carboxamide (6): To a stirring solution of (*R*)-2,3-Difluoropropyl 4-nitrobenzenesulfonate (**54**) (0.41 g, 1.8 mmol, 1.0 equiv) in 1.5 mL MeCN was added carboxamide **22** (0.45 g, 1.6 mmol, 1.1 equiv) and sodium carbonate (0.37 g, 3.5 mmol, 2.2 equiv). The reaction mixture was stirred at 80 °C for 24 h and then allowed to cool to room temperature. The reaction was quenched with saturated $NaHCO_3$ (5 mL) and the mixture extracted with EtOAc (3×20 mL). The collected organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (4:1 to 2:1 hexane/EtOAc) to afford vicinal difluoride **6** (0.41 g, 1.3 mmol, 83%) as a white solid. 97.0% purity by analytical HPLC; 100% purity after preparative HPLC (Reprosil Chiral-NR, heptane/EtOH = 70:30). TLC: $R_f = 0.31$ (3:2 hexane/EtOAc; UV, $KMnO_4$); mp: 158–163 °C; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.08$ (s, 1H), 7.16–7.02 (m, 3H), 5.04–4.79 (m, 1H), 4.73–4.37 (m, 2H), 3.35–3.19 (m, 2H), 3.01 (dd, $J = 10.0$, 3.6 Hz, 1H), 2.49 (ddd, $J = 32.7$, 14.4, 2.1 Hz, 1H), 2.24 (s, 6H), 2.22–2.11 (m, 2H), 1.86–1.69 (m, 3H), 1.66–1.52 (m, 1H), 1.45–1.33 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 172.12$, 135.83, 133.77, 128.43, 127.40, 88.56 (dd, $J = 176.2$, 19.5 Hz), 82.97 (dd, $J = 174.7$, 22.8 Hz), 68.52, 57.12 (dd, $J = 19.8$, 7.0 Hz), 52.48, 30.90, 24.85, 23.44, 18.92 ppm; ^{19}F NMR (377 MHz, $CDCl_3$, decoupled): $\delta = -191.30$ (d, $J = 12.9$ Hz, 1F), −232.87 ppm (d, $J = 13.0$ Hz, 1F); ^{19}F NMR (377 MHz, $CDCl_3$, not decoupled): $\delta =$ −186.47 - −194.55 (m, 1F), −232.87 ppm (tdd, $J = 47.4$, 22.9, 12.9 Hz, 1F); IR (neat): $\tilde{\nu} = 3238$, 2939, 2856, 1715, 1653, 1523, 1499, 1444, 1375, 1232, 1086, 1029, 915, 772, 729 cm^{-1}; HRMS (ESI+) *m/z*: exact mass calculated for $C_{17}H_{25}F_2N_2O$ $[M+H]^+$: 311.1929; found: 311.1934; $[\alpha]_D^{25} = -56.8$ ($c = 1.0$, $CHCl_3$).

(*S*)-1-((*S*)-2,3-Difluoropropyl)-*N*-(2,6-dimethylphenyl)piperidine-2-carboxamide (7): To a stirring solution of (*S*)-2,3-Difluoropropyl 4-nitrobenzenesulfonate (**53**) (0.42 g, 1.5 mmol, 1.0 equiv) in 1.5 mL MeCN was added carboxamide **22** (0.42 g, 1.8 mmol, 1.2 equiv) and sodium carbonate (0.35 g, 3.3 mmol, 2.2 equiv). The reaction mixture was stirred at 80 °C for 12 h and then allowed to cool to room temperature. The reaction was quenched with saturated $NaHCO_3$ (5 mL) and the mixture extracted with EtOAc (3×20 mL). The collected organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (4:1 to 2:1 hexane/EtOAc) to afford vicinal difluoride **7** (0.44 g, 1.4 mmol, 95%) as a white solid. 99.7% purity by analytical HPLC (Reprosil Chiral-NR). TLC: R_f = 0.31 (3:2 hexane/EtOAc; UV, $KMnO_4$); mp: 128–129 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (s, 1H), 7.13–7.05 (m, 3H), 5.02–4.78 (m, 1H), 4.72–4.44 (m, 2H), 3.25–3.17 (m, 1H), 3.16–3.01 (m, 2H), 2.83 (td, J = 14.6, 14.0, 7.2 Hz, 1H), 2.43–2.35 (m, 1H), 2.23 (s, 6H), 2.09–1.98 (m, 1H), 1.94–1.83 (m, 1H), 1.80–1.66 (m, 2H), 1.63–1.39 ppm (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.62, 135.35, 133.72, 128.50, 127.36, 90.88 (dd, J = 174.8, 19.4 Hz), 82.85 (dd, J = 174.3, 23.9 Hz), 67.52, 55.88 (dd, J = 22.6, 6.3 Hz), 52.82 (d, J = 2.1 Hz), 28.87, 24.09, 23.05, 18.93 ppm; ^{19}F NMR (377 MHz, $CDCl_3$, decoupled): δ = −190.74 (d, J = 13.4 Hz, 1F), −232.35 (d, J = 13.5 Hz, 1F); ^{19}F NMR (377 MHz, $CDCl_3$, not decoupled): δ = −190.51–−191.13 (m, 1F), −232.35 ppm (tdd, J = 47.2, 22.0, 13.3 Hz, 1F); IR (neat): $\tilde{\nu}$ = 3224, 2931, 2854, 1654, 1536, 1501, 1477, 1232, 1088, 1065, 1025, 857, 773 cm^{-1}; HRMS (ESI+) m/z: exact mass calculated for $C_{17}H_{25}F_2N_2O$ $[M+H]^+$: 311.1929; found: 311.1932; $[\alpha]_D^{25}$ = −102.8 (c = 1.0, $CHCl_3$).

(*S*)-1-(2,2-Difluoropropyl)-*N*-(2,6-dimethylphenyl)piperidine-2-carboxamide (8): To a suspension of Pd/C (10 wt%) (0.34 g, 0.32 mmol, 0.10 equiv) in 6 mL MeOH was added a solution of (*S*)-benzyl 1-(2,2-difluoropropyl)piperidine-2-carboxylate (**68**) (0.94 g, 3.2 mmol, 1.0 equiv) in 2 mL MeOH. The mixture was flushed with nitrogen and a balloon of hydrogen gas. The reaction mixture was stirred for 4 h under a hydrogen atmosphere, and then filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to obtain a yellow oil. The crude product was dissolved in 8 mL CH_2Cl_2 and Et_3N (0.49 mL, 3.5 mmol, 1.1 equiv) and isobutyl chloroformate (0.47 mL, 3.5 mmol, 1.1 equiv) were added at 0 °C. The reaction mixture was stirred at that temperature for 40 min then 2,6-dimethylaniline (0.48 mL, 3.8 mmol, 1.2 equiv) was added and the mixture was stirred at room temperature for 20 h. The reaction mixture was transferred to a separator funnel and washed with 20 mL 1 M $KHSO_4$, 30 mL saturated $NaHCO_3$ and 20 mL brine. The organic layer was then dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (9:1 to 4:1 hexane/EtOAc) to afford geminal difluoride **8** (0.20 g, 0.64 mmol, 20%) as a white solid. 99.4% purity by analytical HPLC; 100% purity after preparative HPLC (Reprosil Chiral-NR, heptane/EtOH = 70:30). TLC: R_f = 0.43 (4:1 hexane/EtOAc; UV, $KMnO_4$); mp: 171–172 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.38 (s, 1H), 7.13–7.06 (m, 3H), 3.33–3.22 (m, 2H), 3.17–3.04 (m, 1H), 2.95–2.83 (m, 1H), 2.54–2.46 (m, 1H), 2.24 (s, 6H), 2.09–1.99 (m, 1H), 1.97–1.88 (m, 1H), 1.72–1.58 (m, 1H), 1.65 (t, J = 18.5 Hz, 3H), 1.58–1.46 ppm (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.28, 135.42, 128.44, 127.27, 123.58 (t, J = 239.6 Hz), 66.83, 60.97 (t, J = 25.8 Hz), 53.04 (t, J = 1.8 Hz), 26.78, 23.38, 22.60, 22.47 (t, J = 27.0 Hz), 22.20, 18.90 ppm; ^{19}F NMR (377 MHz, $CDCl_3$, decoupled): δ = −94.14 (d, J = 271.70 Hz, 1F), −94.78 ppm (d, J = 271.70 Hz, 1F); ^{19}F NMR (377 MHz, $CDCl_3$, not decoupled): δ = −93.64–−95.29 ppm (m, 2F); IR (neat): $\tilde{\nu}$ = 3306, 2916, 2847, 1663, 1498, 1444, 1128, 1097, 937, 894, 779 cm^{-1}; HRMS (ESI+) m/z: exact mass calculated for $C_{17}H_{25}F_2N_2O$ $[M+H]^+$: 311.1929; found: 311.1932; $[\alpha]_D^{25}$ = −45.6 (c = 1.0, $CHCl_3$).

(*S*)-*N*-(2,6-Dimethylphenyl)-1-(4-fluorobutyl)piperidine-2-carboxamide (9): To a stirring solution of (*S*)-*N*-(2,6-dimethylphenyl)piperidine-2-carboxamide (**22**) (0.25 g, 1.1 mmol, 1.1 equiv) in 1 mL MeCN was added Na_2CO_3 (0.23 g, 3.1 mmol, 1.0 equiv) and 4-fluorobutyl 4-nitrobenzenesulfonate (**34**) (0.44 g, 1.7 mmol, 1.0 equiv) in 1.5 mL MeCN, and the reaction mixture was stirred at 60 °C for 24 h. The reaction mixture was allowed to cool to room temperature and diluted with EtOAc (2 mL). The mixture was extracted with saturated $NaHCO_3$ (3×10 mL) and the organic layer was washed with brine (20 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (4:1 to 1:1 hexane/EtOAc) to give fluoride (**9**) (0.25 g, 0.80 mmol, 82%) as a white solid. 100% purity by analytical HPLC (Lux 5μ Cellulose-2). TLC: R_f = 0.32 (3:2 hexane/EtOAc; UV, $KMnO_4$); mp: 114–116 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (brs, 1H), 7.14–7.03 (m, 3H), 4.45 (dt, J = 47.4, 5.7 Hz, 2H), 3.21 (dtd, J = 11.7, 3.8, 1.2 Hz, 1H), 2.96–2.80 (m, 2H), 2.33 (ddd, J = 11.3, 9.0, 4.1 Hz, 1H), 2.24 (s, 6H), 2.16–2.02 (m, 2H), 1.86–1.58 (m, 7H), 1.59–1.45 (m, 1H), 1.42–1.29 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.89, 135.39, 133.75, 128.49, 127.25, 83.88 (d, J = 165.2 Hz), 68.70, 57.24, 51.70, 30.74, 28.49 (d, J = 19.9 Hz), 24.96, 23.60, 23.60 (d, J = 4.6 Hz), 18.89 ppm; ^{19}F NMR (377 MHz, $CDCl_3$, decoupled): δ = −218.20 ppm (s, 1F); ^{19}F NMR (377 MHz, $CDCl_3$, not decoupled): δ = −217.96–−218.46 ppm (m, 1F); IR (neat): $\tilde{\nu}$ = 3182, 2934, 1768, 1648, 1519, 1469, 1230, 1036, 954, 774 cm^{-1}; HRMS (ESI+) m/z: exact mass calculated for $C_{18}H_{28}FN_2O$ $[M+H]^+$: 307.2180; found: 307.2176; $[\alpha]_D^{25}$ = −108.6 (c = 1.0, $CHCl_3$).

(*S*)-1-(4,4-Difluorobutyl)-*N*-(2,6-dimethylphenyl)piperidine-2-carboxamide (10): To a stirring solution of 4,4-difluorobutyl-4-nitrobenzenesulfonate (**42**) (0.35 g, 1.5 mmol, 1.0 equiv) and (*S*)-*N*-(2,6-dimethylphenyl)piperidine-2-carboxamide (**22**) (0.49 g, 1.7 mmol, 1.1 equiv) in 8 mL MeCN was added K_2CO_3 (0.46 g, 3.3 mmol, 2.2 equiv) in one portion and the mixture was stirred at 80 °C for 13 h. The reaction mixture was then allowed to cool to room temperature and diluted with EtOAc (50 mL). The mixture was extracted with saturated $NaHCO_3$ (3×30 mL), and the organic layer was washed with brine (50 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (4:1 to 1:1 hexane/EtOAc) to give difluoride **10** (0.37 g, 1.1 mmol, 76% yield) as light yellow solid. 100% purity by analytical HPLC (Lux 5μ Cellulose-2). TLC: R_f = 0.27 (3:2 hexane/EtOAc; UV, $KMnO_4$); mp: 99–104 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (s, 1H), 7.15–7.05 (m, 3H), 5.84 (tt, J = 56.5, 3.9 Hz, 1H), 3.20 (dt, J = 10.6, 3.2 Hz, 1H), 2.92 (dd, J = 10.0, 3.6 Hz, 1H), 2.89–2.82 (m, 1H), 2.39–2.30 (m, 1H), 2.24 (s, 6H), 2.15–2.04 (m, 2H), 1.94–1.62 (m, 7H), 1.59–1.46 (m, 1H), 1.42–1.30 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.70, 135.36, 133.68, 128.53, 127.33, 116.94 (t, J = 239.1 Hz), 68.64, 56.71, 51.62, 32.07 (t, J = 21.3 Hz), 30.61, 24.87, 23.55, 20.15 (t, J = 5.1 Hz), 18.89 ppm; ^{19}F NMR (377 MHz, $CDCl_3$, decoupled): δ = −116.02 ppm; ^{19}F NMR (377 MHz, $CDCl_3$, not decoupled): δ = −115.84–−116.20 ppm (m, 2F); IR (neat): $\tilde{\nu}$ = 3251, 2935, 2858, 1658, 1495, 1442, 1404, 1265, 1226, 1121, 1049, 992, 767 cm^{-1}; HRMS (ESI+) m/z: exact mass calculated for $C_{18}H_{27}F_2N_2O_5$ $[M+H]^+$: 325.2086; found: 325.2081; $[\alpha]_D^{25}$ = −89.7 (c = 1.0, $CHCl_3$).

(*S*)-*N*-(2,6-Dimethylphenyl)-1-(4,4,4-trifluorobutyl)piperidine-2-carboxamide (11): To a stirring solution of (*S*)-*N*-(2,6-dimethylphenyl)piperidine-2-carboxamide (**22**) (0.17 g, 0.75 mmol, 1.2 equiv) in 1.5 mL acetonitrile was added Na_2CO_3 (0.15 g, 1.4 mmol, 2.2 mmol) and 3,3,3-trifluoropropyl 4-nitrobenzenesulfonate (**45**) (0.20 g, 0.63 mmol, 1.0 equiv) in 2 mL acetonitrile. The reaction mixture

was stirred at 80 °C for 13 h, then diluted with EtOAc (5 mL) and washed with saturated NaHCO3 (3×20 mL). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (4:1 to 6:4 hexane/EtOAc) to afford trifluoride **11** (0.20 g, 0.57 mmol, 91%) as a white solid. 100% purity by analytical HPLC (Lux 5μ Cellulose-2). TLC: R_f = 0.20 (3:1 hexane/EtOAc; UV, $KMnO_4$); mp: 131–132 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (s, 1H), 7.13–7.05 (m, 3H), 3.22–3.16 (m, 1H), 2.94 (dd, J = 10.0, 3.7 Hz, 1H), 2.87 (ddd, J = 12.6, 10.0, 6.6 Hz, 1H), 2.51–2.30 (m, 1H), 2.24 (s, 6H), 2.18–2.01 (m, 4H), 2.00–1.85 (m, 1H), 1.84–1.68 (m, 4H), 1.54 (td, J = 7.1, 6.2, 3.3 Hz, 1H), 1.44–1.29 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.54, 135.34, 133.64, 128.55, 127.08 (q, J = 276.0 Hz), 68.55, 56.04, 51.57, 31.83 (q, J = 29.1 Hz), 30.43, 24.77, 23.48, 20.27, 18.86 ppm; ^{19}F NMR (377 MHz, $CDCl_3$, decoupled): δ = −66.36 ppm (s, 3F); ^{19}F NMR (377 MHz, $CDCl_3$, not decoupled): δ = −66.36 (t, J = 10.7 Hz, 3F); IR (neat): $\tilde{\nu}$ = 3283, 2943, 2842, 1657, 1496, 1377, 1253, 1147, 1124, 1101, 1055, 1023, 765 cm^{-1}; HRMS (ESI+) m/z: exact mass calculated for $C_{18}H_{26}F_3N_2O_5$ $[M+H]^+$: 343.1992; found: 343.1994; $[\alpha]_D^{25}$ = −72.9 (c = 1.0, $CHCl_3$).

(*S*)-*N*-(2,6-Dimethylphenyl)-1-((*R*)-2-fluorobutyl)piperidine-2-carboxamide (12): To stirring solution of (*S*)-*N*-(2,6-Dimethylphenyl)-1-((*R*)-2-hydroxybutyl)piperidine-2-carboxamide (**63**) (0.73 g, 2.4 mmol, 1.0 equiv) in 12 mL MeCN were added Et_3N (2.00 mL, 14.5 mmol, 6.00 equiv), triethylamine trihydrofluoride (0.83 mL, 4.8 mmol, 2.0 equiv) and nonaflyl fluoride (0.90 mL, 4.8 mmol, 2.0 equiv) at room temperature. The suspension was stirred for 27 h. The reaction was then quenched with saturated $NaHCO_3$ (40 mL) and the mixture extracted with EtOAc (3×30 mL). The collected organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (9:1 to 7:3 hexane/EtOAc) to afford fluoride **12** (0.39 g, 1.3 mmol, 53%) as a white solid. 99.7% purity by analytical HPLC (Reprosil Chiral-NR). TLC: R_f = 0.19 (8:1 EtOAc/hexane; UV, $KMnO_4$); mp: 104–105 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.24 (s, 1H), 7.11–7.03 (m, 3H), 4.79–4.55 (m, 1H), 3.25 (dd, J = 11.3, 4.1 Hz, 1H), 3.15–3.02 (m, 1H), 2.96 (dd, J = 9.9, 3.7 Hz, 1H), 2.37 (dd, J = 35.9, 13.2 Hz, 1H), 2.25 (s, 6H), 2.20–2.07 (m, 1H), 1.84–1.69 (m, 3H), 1.69–1.47 (m, 3H), 1.43–1.30 (m, 1H), 1.00 ppm (t, J = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.59, 135.85, 133.92, 128.38, 127.30, 91.89 (d, J = 170.8 Hz), 68.58, 61.63 (d, J = 19.1 Hz), 52.58, 31.20, 26.67 (d, J = 20.8 Hz), 24.96, 23.59, 19.00 (d, J = 1.4 Hz), 9.52 ppm (d, J = 5.5 Hz); ^{19}F NMR (377 MHz, $CDCl_3$, decoupled): δ = −183.53 ppm (s, 1F); ^{19}F NMR (377 MHz, $CDCl_3$, not decoupled): δ = −183.20–−183.81 ppm (m, 1F); IR (neat): $\tilde{\nu}$ = 3241, 2969, 2936, 1657, 1519, 1476, 1314, 1222, 1097, 923, 893, 765, 715 cm^{-1}; HRMS (ESI+) m/z: exact mass calculated for $C_{18}H_{28}FN_2O$ $[M+H]^+$: 307.2180; found: 307.2185; $[\alpha]_D^{25}$ = −104.3 (c = 1.0, $CHCl_3$).

(*S*)-*N*-(2,6-Dimethylphenyl)-1-((*S*)-2-fluorobutyl)piperidine-2-carboxamide (13): To stirring solution of (*S*)-*N*-(2,6-Dimethylphenyl)-1-((*S*)-2-hydroxybutyl)piperidine-2-carboxamide (**64**) (0.57 g, 1.9 mmol, 1.0 equiv) in 10 mL MeCN were added Et_3N (1.60 mL, 11.2 mmol, 6.00 equiv), triethylamine trihydrofluoride (0.64 mL, 3.7 mmol, 2.0 equiv) and nonaflyl fluoride (0.73 mL, 3.7 mmol, 2.0 equiv) at room temperature. The suspension was stirred for 5 h. The reaction was then quenched with saturated $NaHCO_3$ (40 mL) and the mixture extracted with EtOAc (3×30 mL). The collected organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (9:1 to 7:3 hexane/EtOAc) to afford fluoride **13** (0.19 g, 0.61 mmol, 32%) as a white solid. 99.9% purity by analytical HPLC (Reprosil Chiral-NR). TLC: R_f = 0.15 (8:1 EtOAc/hexane; UV, $KMnO_4$); mp: 117–119 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18 (brs, 1H), 7.12–7.04 (m, 3H), 4.75–4.56 (m, 1H), 3.32–3.25 (m, 1H), 3.10 (dd, J = 8.8, 4.0 Hz, 1H), 2.91 (ddd, J = 31.7, 14.3, 2.9 Hz, 1H), 2.70 (ddd, J = 16.9, 14.3, 7.6 Hz, 1H), 2.37 (ddd, J = 12.4, 9.5, 2.8 Hz, 1H), 2.24 (s, 6H), 2.06–1.98 (m, 1H), 1.92–1.80 (m, 1H), 1.77–1.37 (m, 6H), 1.00 ppm (t, J = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.60, 135.89, 133.96, 128.41, 127.32, 91.93 (d, J = 171.0 Hz), 68.64, 61.69 (d, J = 19.2 Hz), 52.61, 31.26, 26.70 (d, J = 20.8 Hz), 25.02, 23.64, 19.04 (d, J = 1.4 Hz), 9.55 ppm (d, J = 5.5 Hz); ^{19}F NMR (377 MHz, $CDCl_3$, decoupled): δ = −183.55 ppm (s, 1F); ^{19}F NMR (377 MHz, $CDCl_3$, not decoupled): δ = −183.32–−183.77 ppm (m, 1F); IR (neat): $\tilde{\nu}$ = 3181, 3023, 2929, 2856, 1648, 1531, 1474, 1439, 1310, 1232, 766, 719 cm^{-1}; HRMS (ESI+) m/z: exact mass calculated for $C_{18}H_{28}FN_2O$ $[M+H]^+$: 307.2180; found: 307.2183; $[\alpha]_D^{25}$ = −53.4 (c = 0.5, $CHCl_3$).

(*S*)-1-((2*S*,3*R*)-2,3-Difluorobutyl)-*N*-(2,6-dimethylphenyl)piperidine-2-carboxamide (14): To a stirring solution of (2*S*,3*R*)-2,3-difluorobutyl 4-nitrobenzenesulfonate (**85**) (0.18 g, 0.54 mmol, 1.0 equiv) in 5 mL MeCN was added carboxamide **22** (0.15 g, 0.65 mmol, 1.2 equiv) and Na_2CO_3 (0.13 g, 1.2 mmol, 2.2 equiv). The reaction mixture was stirred at 80 °C for 19 h and then allowed to cool to room temperature. The reaction was quenched with saturated $NaHCO_3$ (30 mL) and the mixture extracted with EtOAc (3× 20 mL). The collected organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (4:1 to 3:2 hexane/EtOAc) to afford vicinal difluoride **14** (0.14 g, 0.45 mmol, 83%) as a 5:1 mixture of diastereomers. Further purification by preparative HPLC provided the product as a white solid. 99.7% purity by analytical HPLC (Reprosil Chiral-NR). TLC: R_f = 0.25 (7:3 hexane/EtOAc; UV, $KMnO_4$); mp: 110–112 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = ^{1}H NMR 8.12 (s, 1H), 7.12–7.03 (m, 3H), 4.84–4.58 (m, 2H), 3.27–3.10 (m, 2H), 3.00 (dd, J = 10.0, 3.6 Hz, 1H), 2.63–2.48 (m, 1H), 2.25 (s, 6H), 2.21–2.12 (m, 2H), 1.85–1.70 (m, 3H), 1.65–1.52 (m, 1H), 1.47–1.33 ppm (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.20, 135.83, 133.82, 128.41, 127.35, 91.23 (dd, J = 176.7, 23.9 Hz), 89.18 (dd, J = 171.6, 24.3 Hz), 68.62, 57.22 (dd, J = 19.6, 5.3 Hz), 52.55, 31.06, 24.87, 23.51, 19.08–18.10 (m), 16.44 ppm (dd, J = 22.5, 5.5 Hz); ^{19}F NMR (377 MHz, $CDCl_3$, decoupled): δ = −185.53 (d, J = 14.2 Hz, 1F), −192.06 ppm (d, J = 14.2 Hz, 1F); ^{19}F NMR (377 MHz, $CDCl_3$, not decoupled): δ = −185.31–−185.77 (m, 1F), −191.81–−192.41 ppm (m, 1F); IR (neat): $\tilde{\nu}$ = 3184, 3944, 2859, 1543, 1531, 1474, 1439, 1232, 1009, 990, 769, 780, 722 cm^{-1}; HRMS (ESI+) m/z: exact mass calculated for $C_{18}H_{27}F_2N_2O$ $[M+H]^+$: 325.2086; found: 325.2087; $[\alpha]_D^{25}$ = −12.9 (c = 0.02, $CHCl_3$).

(*S*)-1-((2*R*,3*S*)-2,3-Difluorobutyl)-*N*-(2,6-dimethylphenyl)piperidine-2-carboxamide (15): To a stirring solution of (2*R*,3*S*)-2,3-difluorobutyl 4-nitrobenzenesulfonate (**86**) (0.80 g, 2.7 mmol, 1.0 equiv) in 12 mL MeCN was added carboxamide **22** (0.75 g, 3.2 mmol, 1.2 equiv) and Na_2CO_3 (0.63 g, 6.0 mmol, 2.2 equiv). The reaction mixture was stirred at 80 °C for 48 h and then allowed to cool to room temperature. The reaction was quenched with saturated $NaHCO_3$ (50 mL) and the mixture extracted with EtOAc (3× 40 mL). The collected organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (4:1 to 3:2 hexane/EtOAc) to afford a mixture of 80% **15** and 20% **14**, together (0.79 g, 2.4 mmol, 90%). Further purification by preparative HPLC (Reprosil Chiral-NR, heptane/EtOH = 70:30) provided the product **15** as a white solid of 99% purity. TLC: R_f = 0.25 (7:3 hexane/EtOAc; UV, $KMnO_4$); mp: 141–142 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (brs, 1H), 7.12–7.04 (m, 3H), 4.81–4.55 (m, 2H), 3.33–3.22 (m, 1H), 3.19–3.02 (m, 2H), 2.84–2.69 (m, 1H), 2.46–2.36 (m, 1H), 2.23 (s, 6H), 2.07–1.97 (m, 1H),

1.89 (dtd, J=13.0, 9.0, 8.6, 3.5 Hz, 1H), 1.79–1.64 (m, 2H), 1.61–1.38 (m, 2H), 1.40 ppm (dd, J=24.6, 6.2, 1.8, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=171.68, 135.23, 133.76, 128.45, 127.24, 93.91 (dd, J=176.1, 25.0 Hz), 88.97 (dd, J=171.0, 26.1 Hz), 67.15, 56.46 (dd, J=20.4, 5.0 Hz), 52.82 (d, J=2.8 Hz), 28.62, 24.02, 22.95, 18.92, 16.32 ppm (dd, J=22.4, 5.0 Hz); ^{19}F NMR (377 MHz, $CDCl_3$, decoupled): δ=−183.47 (d, J=14.4 Hz, 1F), −191.82 ppm (d, J=14.4 Hz, 1F); ^{19}F NMR (377 MHz, $CDCl_3$, not decoupled): δ=−183.20–−183.74 (m, 1F), −191.52–−192.08 ppm (m, 1F); IR (neat): $\tilde{\nu}$=3189, 2928, 2854, 1645, 1526, 1473, 1232, 1069, 991, 958, 771, 720, 656 cm^{-1}; HRMS (ESI+) m/z: exact mass calculated for $C_{18}H_{27}F_2N_2O$ $[M+H]^+$: 325.2086; found: 325.2088; $[\alpha]_D^{25}$=−41.0 (c=1.0, $CHCl_3$).

(*S*)-1-((2*R*,3*R*)-2,3-Difluorobutyl)-*N*-(2,6-dimethylphenyl)piperidine-2-carboxamide (16): To a stirring solution of (2*R*,3*R*)-2,3-difluorobutyl 4-nitrobenzenesulfonate (**87**) (0.19 g, 0.66 mmol, 1.0 equiv) in 3 mL MeCN was added carboxamide **22** (0.18 g, 0.79 mmol, 1.2 equiv) and Na_2CO_3 (0.15 g, 1.4 mmol, 2.2 equiv). The reaction mixture was stirred at 80 °C for 48 h and then allowed to cool to room temperature. The reaction was quenched with saturated $NaHCO_3$ (30 mL) and the mixture extracted with EtOAc (3×20 mL). The collected organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (4:1 to 3:2 hexane/EtOAc) to afford a mixture of 91% **16** and 9% **17**, together (0.18 g, 0.56 mmol, 85%). Further purification by preparative HPLC (Reprosil Chiral-NR, heptane/EtOH=70:30) provided the product **16** as a white solid of 100% purity. TLC: R_f=0.25 (7:3 hexane/EtOAc; UV, $KMnO_4$); mp: 145–146 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.07 (brs, 1H), 7.12–7.05 (m, 3H), 4.90–4.51 (m, 2H), 3.24–3.04 (m, 3H), 2.88 (app td, J=14.1, 7.5 Hz, 1H), 2.44–2.34 (m, 1H), 2.24 (s, 6H), 2.09–1.99 (m, 1H), 1.94–1.81 (m, 1H), 1.79–1.65 (m, 2H), 1.61–1.41 (m, 2H), 1.42 ppm (ddd, J=24.0, 6.6, 1.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=135.42, 133.80, 128.47, 127.31, 92.82 (dd, J=178.7, 20.1 Hz), 88.81 (dd, J=174.3, 21.7 Hz), 67.36, 56.12 (dd, J=23.4, 4.5 Hz), 52.73, 28.87, 24.16–23.89 (m), 23.08, 18.92, 16.22 ppm (dd, J=23.2, 5.8 Hz); ^{19}F NMR (377 MHz, $CDCl_3$, decoupled): δ=−191.12 (d, J=9.5 Hz, 1F), −199.73 ppm (d, J=9.5 Hz, 1F); ^{19}F NMR (377 MHz, $CDCl_3$, not decoupled): δ=−191.12 (dpd, J=47.8, 24.0, 9.4 Hz, 1F), −199.51–−199.96 ppm (m, 1F); IR (neat): $\tilde{\nu}$=3328, 2945, 2855, 1651, 1495, 1106, 996, 831, 766, 696 cm^{-1}; HRMS (ESI+) m/z: exact mass calculated for $C_{18}H_{27}F_2N_2O$ $[M+H]^+$: 325.2086; found: 325.2087; $[\alpha]_D^{25}$=−58.9 (c=0.5, $CHCl_3$).

(*S*)-1-((2*S*,3*S*)-2,3-Difluorobutyl)-*N*-(2,6-dimethylphenyl)piperidine-2-carboxamide (17): To a stirring solution of (2*S*,3*S*)-2,3-difluorobutyl 4-nitrobenzenesulfonate (**88**) (0.35 g, 1.2 mmol, 1.0 equiv) in 6 mL MeCN was added carboxamide **22** (0.33 g, 1.4 mmol, 1.2 equiv) and Na_2CO_3 (0.28 g, 2.6 mmol, 2.2 equiv). The reaction mixture was stirred at 80 °C for 19 h and then allowed to cool to room temperature. The reaction was quenched with saturated $NaHCO_3$ (30 mL) and the mixture extracted with EtOAc (3×20 mL). The collected organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (4:1 to 3:2 hexane/EtOAc) to afford a mixture of 92% **17** and 8% **16**, together (0.33 g, 1.0 mmol, 87%). Further purification by preparative HPLC (Reprosil Chiral-NR, heptane/EtOH=70:30) provided the product **17** as a white solid of 99.9% purity. TLC: R_f=0.25 (7:3 hexane/EtOAc; UV, $KMnO_4$); mp: 116–117 °C°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.12 (brs, 1H), 7.11–7.04 (m, 3H), 4.78–4.52 (m, 2H), 3.34 (td, J=14.4, 10.1 Hz, 1H), 3.23 (app dt, J=11.1, 4.0 Hz, 1H), 3.01 (app dd, J=10.2, 3.6 Hz, 1H), 2.56–2.38 (m, 1H), 2.25 (s, 6H), 2.23–2.12 (m, 2H), 1.86–1.70 (m, 3H), 1.66–1.53 (m, 1H), 1.42 (dd, J=23.0, 6.5 Hz, 3H) 1.45–1.31 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=172.23, 135.93, 133.83, 128.41, 127.37, 90.50 (dd, J=180.1, 20.2 Hz), 89.03 (dd, J=174.6, 20.2 Hz), 68.58, 57.81 (dd, J=20.2, 5.7 Hz), 52.48, 31.11, 24.94, 23.52, 18.94, 16.50 ppm (dd, J=23.2, 5.8 Hz); ^{19}F NMR (377 MHz, $CDCl_3$, decoupled): δ=−190.00 (d, J=10.0 Hz, 1F), −199.89 ppm (d, J=10.0 Hz,1F); ^{19}F NMR (377 MHz, $CDCl_3$, not decoupled): δ=−189.73 - −190.27 (m, 1F), −199.67 - −200.17 ppm (m, 1F); IR (neat): $\tilde{\nu}$=3261, 2937, 2857, 1663, 1493, 1041, 990, 787 cm^{-1}; HRMS (ESI+) m/z: exact mass calculated for $C_{18}H_{27}F_2N_2O$ $[M+H]^+$: 325.2086; found: 325.2087; $[\alpha]_D^{25}$=−95.2 (c=0.5, $CHCl_3$).

(*S*)-1-((*S*)-3,4-Difluorobutyl)-*N*-(2,6-dimethylphenyl)piperidine-2-carboxamide (18): To a stirring solution of (*S*)-3,4-difluorobutyl 4-nitrobenzenesulfonate (**60**) (0.45 g, 1.5 mmol, 1.0 equiv) in 6 mL MeCN was added to a stirring solution of carboxamide **22** (0.42 g, 1.8 mmol, 1.2 equiv) and sodium carbonate (0.35 g, 3.3 mmol, 2.2 equiv) in 6 mL MeCN. The reaction mixture was stirred at 80 °C for 14 h and then allowed to cool to room temperature. The reaction was quenched with saturated $NaHCO_3$ (30 mL) and the mixture extracted with EtOAc (3×20 mL). The collected organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (2:1 to 1:2 hexane/EtOAc) to afford vicinal difluoride **18** (0.37 g, 1.1 mmol, 74%) as a white solid. 100% purity by analytical HPLC (Reprosil Chiral-NR). TLC: R_f=0.31 (3:2 hexane/EtOAc; UV, $KMnO_4$); mp: 128–129 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.96 (s, 1H), 7.12–7.05 (m, 3H), 4.95–4.71 (m, 1H), 4.64–4.35 (m, 2H), 3.20–3.10 (m, 1H), 3.08 (dt, J=12.6, 8.4 Hz, 1H), 2.94 (dd, J=10.1, 3.6 Hz, 1H), 2.56–2.42 (m, 1H), 2.24 (s, 6H), 2.18–1.69 (m, 7H), 1.64–1.45 (m, 1H), 1.46–1.30 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=172.46, 135.59, 133.74, 128.49, 127.36, 89.83 (dd, J=173.2, 19.9 Hz), 84.19 (dd, J=174.4, 23.3 Hz), 68.84, 52.21 (d, J=3.1 Hz), 51.41, 30.91, 27.77 (dd, J=20.6, 5.9 Hz), 24.87, 23.64, 18.88 ppm (d, J=1.2 Hz); ^{19}F NMR (377 MHz, $CDCl_3$, decoupled): δ=−190.86 (dd, J=13.5, 1.7 Hz, 1F), −229.72 ppm (d, J=13.5 Hz, 1F); ^{19}F NMR (377 MHz, $CDCl_3$, not decoupled): δ=−190.62–−191.11 (m, 1F), −229.72 ppm (tdd, J=47.5, 21.0, 13.5 Hz, 1F); IR (neat): $\tilde{\nu}$=3290, 2949, 1651, 1488, 1091, 1044, 989, 768 cm^{-1}; HRMS (ESI+) m/z: exact mass calculated for $C_{18}H_{27}F_2N_2O$ $[M+H]^+$: 325.2086; found: 325.2087; $[\alpha]_D^{25}$=−82.1 (c=0.5, $CHCl_3$).

(*S*)-1-((*R*)-3,4-Difluorobutyl)-*N*-(2,6-dimethylphenyl)piperidine-2-carboxamide (19): To a stirring solution of (*R*)-3,4-difluorobutyl 4-nitrobenzenesulfonate (**59**) (0.45 g, 1.5 mmol, 1.0 equiv) in 6 mL MeCN was added to a stirring solution of carboxamide **22** (0.42 g, 1.8 mmol, 1.2 equiv) and sodium carbonate (0.35 g, 3.3 mmol, 2.2 equiv) in 6 mL MeCN. The reaction mixture was stirred at 80 °C for 11 h and then allowed to cool to room temperature. The reaction was quenched with saturated $NaHCO_3$ (30 mL) and the mixture extracted with EtOAc (3×20 mL). The collected organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (2:1 to 1:2 hexane/EtOAc) to afford vicinal difluoride **19** (0.43 g, 1.3 mmol, 86%) as a white solid. 99.9% purity by analytical HPLC (Reprosil Chiral-NR). TLC: R_f=0.31 (3:2 hexane/EtOAc; UV, $KMnO_4$); mp: 110–111 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.02 (s, 1H), 7.12–7.04 (m, 3H), 4.82–4.34 (m, 3H), 3.22–3.16 (m, 1H), 3.11 (ddd, J=12.7, 9.8, 7.1 Hz, 1H), 2.96 (dd, J=9.9, 3.7 Hz, 1H), 2.47–2.39 (m, 1H), 2.25 (s, 6H), 2.18–2.06 (m, 2H), 2.02–1.85 (m, 2H), 1.84–1.68 (m, 3H), 1.61–1.47 (m, 1H), 1.43–1.30 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=172.46, 135.44, 133.67, 128.50, 127.30, 90.49 (dd, J=173.8, 19.8 Hz), 84.06 (dd, J=174.5, 23.3 Hz), 68.46, 53.28 (d, J=4.0 Hz), 51.85, 30.57, 28.49 (dd, J=20.9, 5.9 Hz), 24.86, 23.50, 18.90 ppm (d, J=1.1 Hz); ^{19}F NMR (377 MHz, $CDCl_3$, decoupled): δ=−189.58 (d,

J=13.4 Hz, 1F), −230.46 ppm (dd, J=13.4, 1.8 Hz, 1F); ^{19}F NMR (377 MHz, $CDCl_3$, not decoupled): δ=−189.35–−189.79 (m, 1F), −230.46 ppm (tdd, J=48.0, 21.4, 13.6 Hz, 1F); IR (neat): $\tilde{\nu}$=3164, 2938, 1643, 1519, 1470, 1454, 1227, 1133, 1089, 1034, 961, 861, 710 cm^{-1}; HRMS (ESI+) m/z: exact mass calculated for $C_{18}H_{27}F_2N_2O$ $[M+H]^+$: 325.2086; found: 325.2087; $[\alpha]_D^{25}$=−94.1 (c=0.5, $CHCl_3$).

(*S*)-*N*-(2,6-Dimethylphenyl)piperidine-2-carboxamide (22):[12] To a stirring solution of (*S*)-1-(*tert*-butoxycarbonyl)piperidine-2-carboxylic acid (2.50 g, 10.7 mmol, 1.00 equiv) in 21 mL CH_2Cl_2 was added Et_3N (1.6 mL, 12 mmol, 1.1 equiv) and isobutyl chloroformate (1.6 mL, 12 mmol, 1.1equiv) at 0 °C. After 55 min, 2,6-dimethylaniline (1.67 mL, 13.4 mmol, 1.35 equiv) was added and the reaction mixture was allowed to warm to room temperature. After 24 h the mixture was washed with 1 M $KHSO_4$ (40 mL), saturated $NaHCO_3$ (40 mL) and brine (40 mL). The organic layer was then dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash chromatography (95:5 to 4:1 hexane/EtOAc) to afford the carboxamide (2.77 g, 8.33 mmol, 78% yield) as a light pink solid with some traces of 2,6-dimethylaniline. The solid was then dissolved in 17 mL CH_2Cl_2 and trifluoroacetic acid (3.56 mL, 45.3 mmol, 5.40 equiv) was added dropwise over 15 min. The reaction mixture was stirred for 8.5 h at room temperature, then the solvent was evaporated and water (10 mL) was added. The pH value of the mixture was brought into the range of 10–12 by the addition of 2 M NaOH. The aqueous phase was extracted with CH_2Cl_2 (5×20 mL) and combined organic phases were washed with brine (50 mL), dried over Na_2SO_4 and evaporated in vacuo. The product was isolated as a colorless solid (1.80 g, 7.77 mmol, 93%) and used for the next step without further purification. TLC: R_f=0.37 (9:1 CH_2Cl_2/MeOH; UV, CAM); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.27 (brs, 1H), 7.11–7.03 (m, 3H), 3.44 (dd, J=10.1, 3.4 Hz, 1H), 3.17–3.07 (m, 1H), 2.85–2.73 (m, 1H), 2.22 (s, 6H), 2.13–2.05 (m, 1H), 1.87–1.79 (m, 1H), 1.69–1.56 (m, 2H), 1.49 ppm (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=172.38, 135.25, 133.77, 128.30, 127.16, 60.77, 45.91, 30.47, 26.01, 24.10, 18.67 ppm; IR (neat): $\tilde{\nu}$=3266, 2929, 2852, 1656, 1503, 1474, 1440, 1228, 762 cm^{-1}; HRMS (ESI+) m/z: exact mass calculated for $C_{14}H_{20}N_2O$ $[M+H]^+$, 233.1648; found 23.1650.

Propyl 4-nitrobenzenesulfonate (25): To a stirring solution of propan-1-ol (0.30 mL, 4.0 mmol, 1.0 equiv) in 14 mL CH_2Cl_2 were added Et_3N (1.1 mL, 7.9 mmol, 2.0 equiv), 4-nitrobenzene-1-sulfonyl chloride (1.08 g, 4.77 mmol, 1.20 equiv) and DMAP (50 mg, 0.40 mmol, 0.10 equiv). After stirring for 4 h the, reaction was quenched with saturated NH_4Cl (50 mL) and the mixture extracted with EtOAc (3×40 mL). The collected organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (4:1 to 2:1 hexane/EtOAc) to give nosylate **25** (0.83 g, 3.4 mmol, 85% yield) as a light yellow solid. TLC: R_f=0.45 (4:1 hexane/EtOAc; $KMnO_4$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.44–8.37 (m, 2H), 8.15–8.08 (m, 2H), 4.11 (td, J=6.6, 1.3 Hz, 2H), 1.77–1.67 (m, 2H), 0.92 ppm (td, J=7.4, 1.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=150.85, 142.24, 129.30, 124.58, 73.54, 22.52, 10.04 ppm; IR (neat): $\tilde{\nu}$=3093, 2977, 2871, 1604, 1522, 1349, 1180, 1009, 935, 839, 743, 613 cm^{-1}; HRMS (EI) m/z: exact mass calculated for $C_9H_{11}NO_5S$ $[M]^+$, 245.0358; found 245.0355.

Butyl 4-nitrobenzenesulfonate (26): To a stirring solution of butan-1-ol (0.30 mL, 3.3 mmol, 1.0 equiv) in 14 mL CH_2Cl_2 were added Et_3N (0.50 mL, 3.6 mmol, 1.1 equiv), 4-nitrobenzene-1-sulfonyl chloride (0.96 g, 4.2 mmol, 1.3 equiv) and DMAP (41 mg, 0.33 mmol, 0.10 equiv). The reaction mixture was stirred for 4 h at room temperature. The reaction was then quenched with saturated NH_4Cl (50 mL) and the mixture extracted with EtOAc (3× 40 mL). The collected organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (9:1 hexane/EtOAc) to give nosylate **26** (0.69 g, 2.7 mmol, 82% yield) as a light yellow solid. TLC: R_f=0.48 (4:1 hexane/EtOAc; UV, $KMnO_4$); ^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.43–8.37 (m, 2H), 8.14–8.08 (m, 2H), 4.14 (t, J=6.5 Hz, 2H), 1.72–1.62 (m, 2H), 1.35 (h, J=7.4 Hz, 2H), 0.88 ppm (t, J=7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=150.84, 142.20, 129.30, 124.58, 71.84, 30.93, 18.70, 13.48 ppm; IR (neat): $\tilde{\nu}$=3111, 2963, 2875, 1609, 1540, 1364, 1353, 1314, 1180, 1095, 949, 856, 828, 738, 682, 616 cm^{-1}; HRMS (EI+) m/z: exact mass calculated for $C_{10}H_{13}NO_5S$ $[M]^+$, 259.0514; found 259.0509.

1-Benzyloxy-3-fluoropropane (31):[14] DBU (1.7 mL, 11 mmol, 1.1 equiv) was added to a stirring solution of 3-benzyloxypropan-1-ol (**29**)[13] (1.70 g, 10.2 mmol, 1.00 equiv) in 15 mL THF at 0 °C. After 5 min the mixture was slowly added to a stirring solution of nonaflyl fluoride (2.87 mL, 15.3 mmol, 1.50 equiv) and TBAF(tBuOH)$_4$[15] (7.0 mL, 1.5 mmol, 0.15 equiv, 0.22 M in THF) in 7 mL THF at 0 °C. The reaction mixture was kept at 0 °C for 10 min then allowed to warm to room temperature and stirred for 1 h. The reaction was quenched with saturated $NaHCO_3$ (30 mL) and the mixture extracted with EtOAc (3×30 mL). The organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (4:1 hexane/EtOAc) to yield fluoride (**31**) (1.42 g, 8.44 mmol, 83% yield) as a colorless liquid. TLC: R_f=0.81 (3:1 hexane/EtOAc; UV, CAM); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.39–7.26 (m, 5H), 4.58 (dt, J=47.2, 6.0 Hz, 2H), 4.53 (s, 2H), 3.61 (t, J=6.2 Hz, 2H), 2.01 ppm (dqt, J= 25.7, 6.0 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=138.45, 128.55, 127.77, 127.76, 81.41 (d, J=163.9 Hz), 73.27, 66.12 (d, J=5.6 Hz), 31.05 ppm (d, J=19.8 Hz); ^{19}F NMR (377 MHz, $CDCl_3$, decoupled): δ=−221.68 ppm; ^{19}F NMR (377 MHz, $CDCl_3$, not decoupled): δ= −221.68 ppm (tt, J=47.2, 25.7 Hz); IR (neat): $\tilde{\nu}$=2967, 2852, 1494, 1455, 1364, 1111, 1044, 1001, 953, 733, 690 cm^{-1}; HRMS (EI+) m/z: exact mass calculated for $C_{10}H_{14}O_2$ $[M\text{-}H]^+$, 167.2160; found 167.0867.

1-Benzyloxy-4-fluorobutane (32):[14] DBU (0.42 mL, 2.8 mmol, 1.0 equiv) was added to a stirring solution of 4-benzyloxybutan-1-ol (**30**)[13] (0.50 g, 2.8 mmol, 1.0 equiv) in 20 mL THF at 0 °C. After 5 min the mixture was slowly added to a stirring solution of nonaflyl fluoride (0.78 mL, 4.2 mmol, 1.5 equiv) and TBAF(tBuOH)$_4$[15] (6.30 mL, 1.39 mmol, 0.50 equiv, 0.22 M in THF) in 8 mL THF at 0 °C. The reaction mixture was kept at 0 °C for 10 min then allowed to warm to room temperature and stirred for 1 h. The reaction was quenched with saturated $NaHCO_3$ (30 mL) and the mixture extracted with EtOAc (3×30 mL); then the organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (9:1 to 4:1 hexane/EtOAc) to yield fluoride (**32**) (0.42 g, 2.3 mmol, 84%) as a colorless liquid. TLC: R_f=0.65 (3:1 hexane/EtOAc; UV, CAM); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.38–7.27 (m, 5H), 4.51 (s, 2H), 4.47 (dt, J=47.3, 5.8 Hz, 2H), 3.52 (t, J=6.2 Hz, 2H), 1.89–1.69 ppm (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=138.63, 128.52, 127.75, 127.70, 84.10 (d, J=164.3 Hz), 73.05, 69.84, 27.50 (d, J=19.8 Hz), 25.72 ppm (d, J=5.3 Hz); ^{19}F NMR (377 MHz, $CDCl_3$, decoupled): δ=−218.29; ^{19}F NMR (377 MHz, $CDCl_3$, not decoupled): δ= −218.08–−218.51 ppm (m); IR (neat): $\tilde{\nu}$=3030, 2960, 2856, 1496, 1454, 1362, 1203, 110, 1050, 1028, 992, 953, 736, 697, 668 cm^{-1}; HRMS (EI+) m/z: exact mass calculated for $C_{11}H_{15}FO_2$ $[M]^+$, 182.1107; found 182.1102.

3-Fluoropropyl 4-nitrobenzenesulfonate (33): A 50 mL two-necked flask was loaded with Pd/C (10 wt%) (0.50 g, 0.47 mmol, 0.060 equiv) followed by the addition of 1-benzyloxy-3-fluoropropane (**31**) (1.34 g, 7.97 mmol, 1.00 equiv) in 15 mL CH_2Cl_2. The flask was flushed with nitrogen and one balloon of hydrogen gas. The reaction mixture was stirred at room temperature under a hydrogen atmosphere for 5.5 h. The reaction mixture was then filtered through a pad of Celite and washed with 10 mL CH_2Cl_2. The filtrate was added to a stirring solution of 4-nitrobenzenesulfonyl chloride (2.04 g, 8.76 mmol, 1.10 equiv) in 10 mL CH_2Cl_2 together with Et_3N (2.40 mL, 15.9 mmol, 2.00 equiv) and DMAP (97 mg, 0.80 mmol, 0.10 equiv). The reaction mixture was stirred at room temperature for 2 h. The reaction was then quenched with saturated NH_4Cl (80 mL). The organic phase was separated and concentrated in vacuo. The crude product was purified by flash column chromatography (4:1 to 2:1 hexane/EtOAc) yielding fluoride (**33**) (0.56 mg, 2.1 mmol, 27% yield) as a yellow oil. TLC: $R_f = 0.68$ (3:2 hexane/EtOAc; UV, $KMnO_4$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.45–8.38$ (m, 2H), 8.15–8.09 (m, 2H), 4.50 (dt, $J = 46.8$, 5.6 Hz, 2H), 4.28 (t, $J = 6.1$ Hz, 2H), 2.16–2.03 ppm (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta =$ 150.98, 141.74, 129.38, 124.67, 79.33 (d, $J = 166.6$ Hz), 67.48 (d, $J = 4.6$ Hz), 30.12 ppm (d, $J = 20.2$ Hz); ^{19}F NMR (377 MHz, $CDCl_3$, decoupled): $\delta = -223.86$ ppm; ^{19}F NMR (377 MHz, $CDCl_3$, not decoupled): $\delta = -223.86$ ppm (tt, $J = 46.8$, 25.9 Hz); IR (neat): $\tilde{\nu} = 2919$, 2952, 1527, 1350, 1183, 910, 743 cm^{-1}; HRMS (EI+) *m/z*: exact mass calculated for $C_9H_{10}FNO_5S$ $[M]^+$, 263.0264; found 263.0255.

4-Fluorobutyl 4-nitrobenzenesulfonate (34): A 25 mL two-necked flask was loaded with Pd/C (10 wt%) (0.51 g, 0.24 mmol, 0.060 equiv) followed by the addition of 1-benzyloxy-4-fluorobutane (**32**) (0.80 g, 4.0 mmol, 1.0 equiv) in 10 mL CH_2Cl_2. The flask was flushed with nitrogen and one balloon of hydrogen gas. The reaction mixture was stirred at room temperature under a hydrogen atmosphere for 1.5 h. The reaction mixture was then filtered through a pad of Celite and washed with 3 mL CH_2Cl_2. The filtrate was added to a stirring solution of 4-nitrobenzenesulfonyl chloride (1.08 g, 4.79 mmol, 1.20 equiv) in 10 mL CH_2Cl_2 together with Et_3N (1.11 mL, 7.99 mmol, 2.00 equiv) and DMAP (49 mg, 0.40 mmol, 0.10 equiv). The reaction mixture was stirred at room temperature for 2 h. The reaction was then quenched with saturated NH_4Cl (40 mL) and the organic phase was separated and concentrated in vacuo. The crude product was purified by flash column chromatography (9:1 to 7:3 hexane/EtOAc) yielding fluoride **34** (0.67 g, 2.4 mmol, 60%) as a light yellow oil. TLC: $R_f = 0.4$ (3:1 hexane/EtOAc; UV, $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.44–8.39$ (m, 2H), 8.14–8.09 (m, 2H), 4.44 (dt, $J = 47.4$, 5.6 Hz, 2H), 4.20 (t, $J = 6.2$ Hz, 2H), 1.91–1.69 ppm (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta =$ 150.93, 142.00, 129.34, 124.64, 83.18 (d, $J = 165.7$ Hz), 71.33 (d, $J = 1.1$ Hz), 26.56 (d, $J = 20.2$ Hz), 25.47 ppm (d, $J = 4.3$ Hz); ^{19}F NMR (377 MHz, $CDCl_3$, decoupled): $\delta = -219.50$ ppm; ^{19}F NMR (377 MHz, $CDCl_3$, not decoupled): $\delta = -219.50$ ppm (tt, $J = 47.4$, 26.5 Hz); IR (neat): $\tilde{\nu} = 3101$, 2977, 1609, 1529, 1371, 1348, 1180, 1029, 957, 944, 902, 816, 747, 737, 682 cm^{-1}; HRMS (EI+) *m/z*: exact mass calculated for $C_6H_6NO_5S$ [*M*-C4H6F]$^+$: 203.9967; found: 203.9962.

3-Trityloxypropanal (37): A solution of 3-trityloxypropan-1-ol (**35**)[16] (1.00 g, 3.14 mmol, 1.00 equiv) in 3 mL CH_2Cl_2 was added in one portion, at room temperature, to a stirred suspension of PCC (1.01 g, 4.71 mmol, 1.50 equiv) and Celite (1.00 g) in 9 mL CH_2Cl_2. The resulting dark-brown reaction mixture was stirred for 3 h at room temperature, then diluted with diethyl ether (10 mL) and filtered through a short pad of Celite. The filtrate was concentrated and the crude residue purified by flash column chromatography (9:1 to 4:1 hexane/EtOAc) to afford aldehyde **37** (0.65 g, 2.1 mmol, 66% yield) as colorless solid. TLC: $R_f = 0.51$ (4:1 hexane/EtOAc; UV, $KMnO_4$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.81–9.78$ (m, 1H), 7.52–7.44 (m, 6H), 7.39–7.32 (m, 6H), 7.32–7.25 (m, 3H), 3.52 (q, $J = 6.0$ Hz, 2H), 2.68 ppm (t, $J = 6.1$ Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta =$ 201.70, 143.90, 128.74, 128.01, 127.25, 87.09, 58.03, 44.20 ppm; IR (neat): $\tilde{\nu} = 3040$, 2881, 2724, 1719, 1489, 1449, 1214, 1150, 1077, 905, 748, 699, 638, 409 cm^{-1}; HRMS (EI+) *m/z*: exact mass calculated for $C_{22}H_{20}O_2$ $[M]^+$: 316.1463; found: 316.1458.

1-Trityloxy-3,3-difluoropropane (39): To a solution of 3-(trityloxy-propanal (**37**) (3.54 g, 11.2 mmol, 1.00 equiv) stirring in 33 mL CH_2Cl_2 at 0 °C under N_2 atmosphere was dropwise added DAST (3.11 mL, 22.4 mmol, 2.00 equiv) followed by one drop of ethanol. After 10 min the reaction mixture was allowed to warm to room temperature and stirred for another 20 min. The reaction mixture was then cooled to 0 °C, diluted with 10 mL CH_2Cl_2, and the reaction carefully quenched with 5 mL saturated $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (3×50 mL), and the organic layers dried over Na_2SO_4 and concentrated in vacuo. The crude yellow residue was purified by flash column chromatography (100:1 to 9:1 hexane/EtOAc) to give difluoride **39** (3.84 g, 10.0 mmol, 89% yield) as a white solid. TLC: $R_f = 0.77$ (9:1 hexane/EtOAc; UV, CAM); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.50–7.41$ (m, 6H), 7.38–7.23 (m, 9H), 6.11 (app tq, $J = 56.9$, 4.5 Hz, 1H), 3.33–3.27 (m, 3H), 2.19–2.04 ppm (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 143.92$, 128.70, 128.01, 127.26, 116.26 (t, $J = 238.4$ Hz), 87.04, 57.84 (t, $J = 6.8$ Hz), 35.13 ppm (t, $J = 21.4$ Hz); ^{19}F NMR (377 MHz, $CDCl_3$, decoupled): $\delta = -116.96$–-117.01 ppm (m, 2F); ^{19}F NMR (377 MHz, $CDCl_3$, not decoupled): $\delta = -116.83$ - -117.13 ppm (m, 2F); IR (neat): $\tilde{\nu} = 3077$, 2989, 2930, 2881, 1597, 1489, 1440, 1381, 1090, 1031, 1002, 977, 761, 703 cm^{-1}; HRMS (EI+) *m/z*: exact mass calculated for $C_{22}H_{20}F_2O$ $[M]^+$: 338.1482; found: 338.1477.

3,3-Difluoropropyl 4-nitrobenzenesulfonate (40): 1-Trityloxy-3,3-difluoropropane (**39**) (3.38 g, 10.0 mmol) was dissolved in 18 mL CH_2Cl_2 and cooled to 0 °C. After 5 min HCl (10.0 mL, 20.0 mmol, 2.00 equiv, 2 M in Et_2O) was added dropwise and the mixture was stirred at room temperature for 24 h. The solvent was then removed by distillation and the intermediate product collected in a second fraction ($T_{bp} = 120$ °C, 1 atm). The isolated product was dissolved in 30 mL CH_2Cl_2 followed by the addition of Et_3N (2.79 mL, 20.0 mmol, 2.00 equiv), DMAP (61 mg, 0.50 mmol, 0.050 equiv) and 4-nitrobenzenesulfonyl chloride (2.50 g, 11.0 mmol, 1.10 equiv). The reaction mixture was stirred at room temperature for 1.5 h. The reaction was then quenched with saturated $NaHCO_3$ (30 mL) and the mixture extracted with EtOAc (3× 30 mL). The collected organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (9:1 to 6:1 hexane/EtOAc) to afford difluoride **40** (0.16 g, 0.56 mmol, 6% yield) as yellow solid. TLC: $R_f =$ 0.52 (7:3 hexane/EtOAc; UV, $KMnO_4$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 8.45–8.40 (m, 2H), 8.15–8.10 (m, 2H), 5.92 (tt, $J = 55.8$, 4.3 Hz, 1H), 4.31 (t, $J = 6.1$ Hz, 2H), 2.28 ppm (ttd, $J = 16.3$, 6.1, 4.3 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 151.10$, 141.40, 129.44, 124.75, 114.27 (t, $J = 239.9$ Hz), 65.01 (t, $J = 7.0$ Hz), 33.93 ppm (t, $J =$ 22.7 Hz); ^{19}F NMR (377 MHz, $CDCl_3$, decoupled): $\delta = -118.44$ ppm (s, 2F); ^{19}F NMR (377 MHz, $CDCl_3$, not decoupled): $\delta = -118.44$ ppm (dt, $J = 55.8$, 16.3 Hz, 2F); IR (neat): $\tilde{\nu} = 3111$, 1531, 1350, 1311, 1180, 1095, 1014, 969, 923, 856, 836, 777, 745, 733, 684 cm^{-1}; HRMS (EI+) *m/z*: exact mass calculated for $C_9H_9F_2NO_2S$ $[M]^+$: 281.0169; found: 281.0164.

1-Benzoyloxy-4,4-difluorobutane (41): To a solution of 4-benzoyloxybutanal (**38**)[18] (4.15 g, 21.6 mmol, 1.00 equiv) stirring in 54 mL CH_2Cl_2 at 0 °C under an N_2 atmosphere was dropwise added DAST

(5.40 mL, 38.9 mmol, 1.80 equiv). After 10 min the reaction mixture was allowed to warm to room temperature and stirred for another 50 min. The reaction was then carefully quenched with saturated $NaHCO_3$ (20 mL) at 0 °C, and the reaction mixture extracted with CH_2Cl_2 (3×20 mL). The collected organic layers were dried over Na_2SO_4 and the solvent was concentrated in vacuo. The crude yellow compound was purified by flash column chromatography (95:5 to 9:1 hexane/EtOAc) to give difluoride **41** (3.88 g, 18.1 mmol, 84% yield) as a colorless liquid. TLC: R_f = 0.61 (4:1 hexane/EtOAc; UV, CAM); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07–8.01 (m, 2H), 7.61–7.54 (m, 1H), 7.45 (dd, J = 8.3, 7.0 Hz, 2H), 5.91(tt, J = 56.6, 4.2 Hz,1H), 4.38 (t, J = 6.0 Hz, 2H), 2.10–1.91 ppm (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.57, 133.20, 130.20, 129.68, 128.56, 116.89 (t, J = 239.1 Hz), 64.00, 31.13 (t, J = 21.5 Hz), 21.75 ppm (t, J = 5.6 Hz); ^{19}F NMR (377 MHz, $CDCl_3$, decoupled): δ = −116.28 ppm; ^{19}F NMR (377 MHz, $CDCl_3$, not decoupled): δ = −116.28 ppm (dt, J = 56.5, 16.9 Hz, 2F); IR (neat): $\tilde{\nu}$ = 3069, 2964, 2887, 1715, 1600, 1447, 1409, 1313, 1274, 1179, 1116, 1064, 1025, 973, 704 cm^{-1}; HRMS (ESI+) m/z: exact mass calculated for $C_{11}H_{13}F_2O_2$ $[M+H]^+$: 215.0878; found: 215.0878.

4,4-Difluorobutyl 4-nitrobenzenesulfonate (42): Solid sodium methoxide (1.52 g, 27.1 mmol, 1.50 equiv) was added in one portion to a stirring solution of 1-benzoyloxy-4,4-difluorobutane (**41**) (3.87 g, 18.1 mmol, 1.00 equiv) in 36 mL MeOH at 0 °C. After 1.5 h TFA (2.13 mL, 27.1 mmol, 1.50 equiv) was added and the clear reaction mixture was stirred for another 30 min. Methanol was then removed under reduced pressure and the residue partitioned between Et_2O (20 mL) and brine (50 mL). The aqueous layer was extracted with Et_2O (3×20 mL) and the collected organic phases were concentrated in vacuo. The crude product was dissolved again in 40 mL CH_2Cl_2 followed by the addition of Et_3N (3.00 mL, 21.5 mmol, 1.20 equiv), 4-nitrobenzenesulfonyl chloride (4.00 g, 17.7 mmol, 1.00 equiv) and DMAP (0.11 g, 0.90 mmol, 0.05 equiv). The reaction mixture was stirred at room temperature for 1.5 h. The reaction was then quenched with saturated NH_4Cl (70 mL) and the mixture extracted with EtOAc (3×40 mL). The collected organic phases were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (9:1 to 7:3 hexane/EtOAc) to afford difluoride **42** (2.73 g, 9.25 mmol, 51% yield) as a yellow oil. TLC: R_f = 0.40 (3:2 hexane/EtOAc; UV, $KMnO_4$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.45–8.39 (m, 2H), 8.15–8.09 (m, 2H), 5.84 (tt, J = 56.2, 3.6 Hz, 1H), 4.20 (t, J = 6.0 Hz, 2H), 2.01–1.84 ppm (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 151.00, 141.82 129.35, 124.69, 116.27 (t, J = 239.4 Hz), 70.59, 30.20 (t, J = 21.7 Hz), 21.83 ppm (t, J = 5.5 Hz); ^{19}F NMR (377 MHz, $CDCl_3$, decoupled): δ = −116.75 ppm; ^{19}F NMR (377 MHz, $CDCl_3$, not decoupled): δ = −116.75 ppm (dt, J = 56.3, 17.4 Hz, 2F); IR (neat): $\tilde{\nu}$ = 3069, 2964, 2887, 1715, 1600, 1447, 1409, 1313, 1274, 1179, 1116, 1064, 1025, 973, 704 cm^{-1}; HRMS (ESI+) m/z: exact mass calculated for $C_{18}H_{26}F_2NO_5S[M]^+$: 295.0326; found: 295.0321.

3,3,3-Trifluoropropyl 4-nitrobenzenesulfonate (45): To a stirring solution of 3,3,3-trifluoropropan-1-ol **43** (0.20 mL, 2.3 mmol, 1.0 equiv) in 5 mL CH_2Cl_2 were added 4-nitrobenzene-1-sulfonyl chloride (0.60 g, 2.7 mmol, 1.2 equiv) and Et_3N (0.63 mL, 4.5 mmol, 2.0 equiv). The reaction mixture was stirred at room temperature for 15 min. The reaction was then quenched with saturated NH_4Cl (3 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (20:1 to 4:1 hexane/EtOAc) to afford trifluoride **45** (0.67 g, 2.3 mmol, 99% yield) as a yellow oil. TLC: R_f = 0.51 (3:1 hexane/EtOAc; UV, $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.46–8.40 (m, 2H), 8.15–8.10 (m, 2H), 4.35 (t, J = 6.2 Hz, 2H), 2.57 ppm (qt, J = 10.0, 6.2 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 151.14, 141.29, 129.46, 125.03 (q, J = 276.9 Hz), 124.74, 63.49 (d, J = 3.8 Hz), 33.93 ppm (q, J = 30.1 Hz); ^{19}F NMR (377 MHz, $CDCl_3$, decoupled): δ = −64.96 ppm (s, 3F); ^{19}F NMR (377 MHz, $CDCl_3$, not decoupled): δ = −64.96 ppm (t, J = 10.0 Hz, 3F); IR (neat): $\tilde{\nu}$ = 3110, 1612, 1545, 1430, 1397, 1368, 1349, 1249, 1182, 1153, 1134, 901, 918, 856, 704, 692 cm^{-1}; HRMS (EI+) m/z: exact mass calculated for $C_9H_8F_3NO_5S$ $[M]^+$: 299.0075; found: 299.0070.

4,4,4-Trifluorobutyl 4-nitrobenzenesulfonate (46): To a stirring solution of 4,4,4-trifluorobutan-1-ol **44** (0.10 mL, 0.93 mmol, 1.0 equiv) in 4.5 mL CH_2Cl_2 were added 4-nitrobenzene-1-sulfonyl chloride (0.29 g, 1.3 mmol, 1.4 equiv) and Et_3N (0.26 mL, 1.9 mmol, 2.0 equiv). The reaction mixture was stirred at room temperature for 1 h. The reaction was then quenched with saturated NH_4Cl (3 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (20:1 to 4:1 hexane/EtOAc) to afford trifluoride **46** (0.26 g, 0.82, 88% yield) as a light yellow oil. TLC: R_f = 0.40 (4:1 hexane/EtOAc; UV, $KMnO_4$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.47–8.34 (m, 2H), 8.17–8.07 (m, 2H), 4.21 (t, J = 6.1 Hz, 2H), 2.27–2.14 (m, 2H), 2.03–1.95 ppm (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 151.06, 141.66, 129.38, 126.59 (q, J = 276.2 Hz), 124.73, 69.57, 30.19 (q, J = 29.7 Hz), 22.19 ppm (q, J = 3.1 Hz); ^{19}F NMR (377 MHz, $CDCl_3$, decoupled): δ = −66.26 ppm (s, 3F); ^{19}F NMR (377 MHz, $CDCl_3$, not decoupled): δ = −66.26 ppm (t, J = 10.2 Hz, 3F); IR (neat): $\tilde{\nu}$ = 3100, 1539, 1368, 1351, 1255, 1185, 1154, 992, 904, 856, 822, 720, 614 cm^{-1}; HRMS (EI+) m/z: exact mass calculated for $C_{10}H_{10}F_3NO_5S$ $[M]^+$: 313.0232; found: 313.0227.

(*S*)-1-Benzyl-2,3-difluoropropane (51): Triethylamine trihydrofluoride (1.00 mL, 6.01 mmol, 0.630 equiv) was added to (*R*)-2-((benzyloxy)methyl)oxirane **49**[19] (1.56 g, 9.48 mmol, 1.00 equiv), then the vessel was sealed and the mixture was heated at 150 °C and stirred for 1.5 h. The reaction was then quenched with water (10 mL) and the mixture extracted with EtOAc (3×30 mL). The collected organic layers were washed with saturated $NaHCO_3$ (50 mL), dried over Na_2SO_4 and concentrated in vacuo. The obtained mixture of regioisomers was used for the next step without further purification. The crude mixture was dissolved in 15 mL THF together with DBU (1.59 mL, 10.4 mmol, 1.10 equiv) and slowly added to a stirring solution of nonaflyl fluoride (3.19 mL, 17.07 mmol, 1.80 equiv) stirring in 30 mL THF at 0 °C. After 10 min the reaction mixture was allowed to warm to room temperature and stirred for an additional 50 min. The reaction was quenched with saturated $NaHCO_3$ (100 mL) and the mixture extracted with EtOAc (3×50 mL). The collected organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (20:1 to 9:1 hexane/EtOAc) to afford vicinal difluoride **51** (1.02 g, 5.46 mmol, 58%) as a colorless liquid. TLC: R_f = 0.75 (4:1 hexane/EtOAc; UV, CAM); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.28 (m, 5H), 4.95–4.73 (m, 1H), 4.63 (ddd, J = 47.3, 24.0, 4.0 Hz, 2H), 4.59 (s, 2H), 3.72 ppm (ddd, J = 19.9, 5.0, 1.3 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 137.59, 128.65, 128.08, 127.86, 90.51 (dd, J = 175.6, 19.8 Hz), 82.31 (dd, J = 172.3, 23.3 Hz), 73.84, 67.97 ppm (dd, J = 24.3, 8.0 Hz); ^{19}F NMR (377 MHz, $CDCl_3$, decoupled): δ = −196.14 (d, J = 13.3, 1F), −233.71 ppm (d, J = 13.3 Hz, 1F); ^{19}F NMR (377 MHz, $CDCl_3$, not decoupled): δ = −195.93 - −196.37 (m, 1F), −233.70 ppm (tdd, J = 47.3, 21.2, 13.2 Hz, 1F); IR (neat): $\tilde{\nu}$ = 2865, 1496, 1453, 1251, 1094, 1027, 912, 856, 737, 698 cm^{-1}; HRMS (EI+) m/z: exact mass calculated for $C_{10}H_{12}F_2O_2$ $[M]^+$: 186.0856; found: 186.0851.

(*R*)-1-Benzyloxy-2,3-difluoropropane (52): Triethylamine trihydrofluoride (1.00 mL, 6.01 mmol, 0.820 equiv) was added to (*S*)-2-

((benzyloxy)methyl)oxirane **50**[19] (1.20 g, 7.31 mmol, 1.00 equiv), then the vessel was sealed and the mixture was heated at 150 °C and stirred for 1.5 h. The reaction was then quenched with water (10 mL) and the mixture extracted with EtOAc (3×40 mL). The collected organic layers were washed with saturated $NaHCO_3$ (50 mL), dried over Na_2SO_4 and concentrated in vacuo. The obtained mixture of regioisomers was used for the next step without further purification. The crude mixture was dissolved in 10 mL THF together with DBU (1.30 mL, 8.04 mmol, 1.10 equiv) and slowly added to a stirring solution of nonaflyl fluoride (2.46 mL, 13.1 mmol, 1.80 equiv) stirring in 30 mL THF at 0 °C. After 10 min the reaction mixture was allowed to warm to room temperature and stirred for an additional 50 min. The reaction was quenched with saturated $NaHCO_3$ (100 mL) and the mixture extracted with EtOAc (3× 50 mL). The collected organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (20:1 to 9:1 hexane/EtOAc) to afford vicinal difluoride **52** (0.91 g, 4.9 mmol, 67%) as a colorless liquid. TLC: R_f = 0.75 (4:1 hexane/EtOAc; UV, CAM); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.28 (m, 5H), 4.95–4.73 (m, 1H), 4.63 (ddd, J = 47.3, 24.0, 3.9 Hz, 2H), 4.59 (s, 2H), 3.72 ppm (ddd, J = 19.9, 5.0, 1.3 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 137.59, 128.66, 128.09, 127.87, 90.52 (dd, J = 175.6, 19.8 Hz), 82.31 (dd, J = 172.3, 23.3 Hz), 73.85, 67.98 ppm (dd, J = 24.3, 8.0 Hz); ^{19}F NMR (377 MHz, $CDCl_3$, decoupled): δ = −196.15 (d, J = 13.2 Hz, 1F), −233.71 ppm (d, J = 13.2 Hz, 1F); ^{19}F NMR (377 MHz, $CDCl_3$, not decoupled): δ = −195.94 - −196.37 (m, 1F), −233.71 ppm (tdd, J = 47.3, 21.3, 13.1 Hz, 1F); IR (neat): $\tilde{\nu}$ = 3033, 2866, 1454, 1364, 1107, 1029, 916, 856, 740, 698, 668 cm^{-1}; HRMS (EI+) m/z: exact mass calculated for $C_{10}H_{12}F_2O_2$ $[M]^+$: 186.0856; found: 186.0851.

(*S*)-2,3-Difluoropropyl 4-nitrobenzenesulfonate (53): A solution of (*S*)-1-benzyloxy-2,3-difluoropropane (**51**) (1.00 g, 5.37 mmol, 1.00 equiv) in 6.3 mL THF was added to a 25 mL two-necked flask loaded with Pd/C (10 wt%) (0.80 g, 0.38 mmol, 0.070 equiv). The flask was flushed with nitrogen and one balloon of hydrogen. The reaction mixture was stirred at room temperature under a hydrogen atmosphere for 2 h then filtered through a pad of Celite. The filtrate was diluted with 4 mL CH_2Cl_2 followed by the addition of 4-nitrobenzene-1-sulfonyl chloride (1.58 g, 6.98 mmol, 1.30 equiv), Et_3N (1.50 mL, 10.7 mmol, 2.00 equiv) and DMAP (66 mg, 0.54 mmol, 0.10 equiv). The reaction mixture was stirred for 4 h. The reaction was then quenched with $NaHCO_3$ (10 mL) and the mixture extracted with EtOAc (3×20 mL). The collected organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (9:1 to 7:3 hexane/EtOAc) to afford vicinal difluoride **53** (1.20 g, 4.27 mmol, 79%) as a yellow solid. TLC: R_f = 0.55 (3:1 hexane/EtOAc; UV, $KMnO_4$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.47–8.38 (m, 2H), 8.17–8.09 (m, 2H), 4.99–4.75 (m, 1H), 4.73–4.45 (m, 2H), 4.47–4.32 ppm (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 151.14, 141.19, 129.50, 124.74, 87.97 (dd, J = 180.3, 20.9 Hz), 80.68 (dd, J = 174.6, 24.3 Hz), 68.03 ppm (dd, J = 25.1, 8.0 Hz); ^{19}F NMR (377 MHz, $CDCl_3$, decoupled): δ = −197.05 (d, J = 13.7 Hz, 1F), −235.40 ppm (d, J = 13.7 Hz, 1F); ^{19}F NMR (377 MHz, $CDCl_3$, not decoupled): δ = −196.84 - −197.26 (m, 1F), −235.40 ppm (tdd, J = 46.8, 21.2, 13.7 Hz, 1F); IR (neat): $\tilde{\nu}$ = 3117, 1533, 1370, 1349, 1309, 1190, 1060, 997, 921, 874, 815, 740, 684, 666, 619 cm^{-1}; HRMS (EI+) m/z: exact mass calculated for $C_9H_9F_2NO_5S$ $[M]^+$: 281.0169; found: 281.0164.

(*R*)-2,3-Difluoropropyl 4-nitrobenzenesulfonate (54): A solution of (*R*)-1-Benzyloxy-2,3-difluoropropane (**52**) (0.86 g, 4.6 mmol, 1.0 equiv) in 6.3 mL THF was added to a 25 mL two-necked flask loaded with Pd/C (10 wt%) (0.50 g, 0.23 mmol, 0.050 equiv). The flask was flushed with nitrogen and one balloon of hydrogen. The reaction mixture was stirred at room temperature under a hydrogen atmosphere for 2.5 h then filtered through a pad of Celite. The filtrate was diluted with 4 mL CH_2Cl_2 followed by the addition of 4-nitrobenzene-1-sulfonyl chloride (1.40 g, 6.50 mmol, 1.40 equiv), Et_3N (1.29 mL, 9.28 mmol, 2.00 equiv) and DMAP (57 mg, 0.46 mmol, 0.10 equiv). The reaction mixture was stirred for 4 h. The reaction was then quenched with $NaHCO_3$ (10 mL) and the mixture extracted with EtOAc (3×20 mL). The collected organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (9:1 to 7:3 hexane/EtOAc) to afford vicinal difluoride **54** (1.11 g, 3.95 mmol, 85%) as a yellow solid. TLC: R_f = 0.55 (3:1 hexane/EtOAc; UV, $KMnO_4$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.46–8.39 (m, 2H), 8.17–8.09 (m, 2H), 4.99–4.75 (m, 1H), 4.73–4.45 (m, 2H), 4.47–4.32 ppm (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 151.13, 141.17, 129.49, 124.73, 87.98 (dd, J = 180.3, 20.9 Hz), 80.69 (dd, J = 174.5, 24.2 Hz), 68.04 ppm (dd, J = 25.1, 8.0 Hz); ^{19}F NMR (377 MHz, $CDCl_3$, decoupled): δ = −197.04 (d, J = 13.7 Hz, 1F), −235.39 ppm (d, J = 13.6 Hz, 1F); ^{19}F NMR (377 MHz, $CDCl_3$, not decoupled): δ = −195.93 - −196.37 (m, 1F), −233.70 ppm (tdd, J = 47.3, 21.2, 13.2 Hz, 1F); IR (neat): $\tilde{\nu}$ = 3099, 1528, 1371, 1348, 1309, 1190, 1107, 1094, 1015, 944, 921, 873, 813, 739, 683, 667, 617 cm^{-1}; HRMS (EI+) m/z: exact mass calculated for $C_9H_9F_2NO_5S$ $[M]^+$: 281.0169; found: 281.0164.

(*R*)-1-Benzyloxy-3,4-difluorobutane (57): A mixture of triethylamine trihydrofluoride (0.51 mL, 3.1 mmol, 0.50 equiv) and (*S*)-2-(2-benzyloxyethyl)oxirane **55**[20] (1.10 g, 6.17 mmol, 1.00 equiv) was stirred in a sealed vessel at 150 °C for 2 h. The reaction was then quenched with water (10 mL) and the mixture extracted with EtOAc (3×20 mL). The collected organic layers were dried over Na_2SO_4 and evaporated in vacuo. The crude product was then dissolved in 18 mL THF followed by the addition of nonaflyl fluoride (2.31 mL, 12.3 mmol, 2.00 equiv), triethylamine trihydrofluoride (2.05 mL, 12.3 mmol, 2.00 equiv) and Et_3N (5.16 mL, 37.0 mmol, 6.00 equiv). The reaction mixture was stirred at room temperature for 3 h. The reaction was then quenched with saturated $NaHCO_3$ (50 mL) and the mixture extracted with Et_2O (3×50 mL). The collected organic layers were washed with brine, dried over Na_2SO_3 and concentrated in vacuo. The crude product was purified by flash column chromatography (9:1 hexane/Et_2O) to afford vicinal difluoride **57** (1.02 g, 3.47 mmol, 56%) as colorless liquid. TLC: R_f = 0.8 (7:3 hexane/EtOAc; UV, CAM); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.27 (m, 5H), 5.04–4.79 (m, 1H), 4.71–4.34 (m, 2H), 4.52 (s, 2H), 3.67–3.60 (m, 2H), 2.08–1.85 ppm (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.20, 128.60, 127.88, 127.79, 89.58 (dd, J = 172.4, 19.2 Hz), 84.43 (dd, J = 173.5, 22.0 Hz), 73.34, 65.44 (d, J = 5.4 Hz), 30.74 ppm (dd, J = 21.1, 6.8 Hz); ^{19}F NMR (377 MHz, $CDCl_3$, decoupled): δ = −191.13 (d, J = 12.9 Hz, 1F), −229.86 ppm (d, J = 12.9 Hz, 1F); ^{19}F NMR (377 MHz, $CDCl_3$, not decoupled): δ = −190.90–−191.36 (m), −229.86 ppm (tdd, J = 47.6, 22.3, 12.9 Hz); IR (neat): $\tilde{\nu}$ = 3032, 2864, 1496, 1454, 1363, 1099, 1027, 1002, 859, 738, 698 cm^{-1}; HRMS (EI+) m/z: exact mass calculated for $C_{11}H_{13}F_2O$ $[M-H]^+$: 199.0934; found: 199.0929.

(*S*)-1-Benzyloxy-3,4-difluorobutane (58): A mixture of triethylamine trihydrofluoride (0.46 mL, 2.8 mmol, 0.50 equiv) and (*R*)-2-(2-benzyloxyethyl)oxirane **56**[20] (0.98 g, 5.5 mmol, 1.0 equiv) was stirred in a sealed vessel at 150 °C for 1.5 h. The reaction was then quenched with water (10 mL) and the mixture extracted with EtOAc (3×20 mL). The collected organic layers were dried over Na_2SO_4 and evaporated in vacuo. The crude product was then dissolved in 16 mL THF followed by the addition of nonaflyl fluoride (2.06 mL, 11.0 mmol, 2.00 equiv), triethylamine trihydrofluoride

(1.83 mL, 11.0 mmol, 2.00 equiv) and Et_3N (4.61 mL, 33.1 mmol, 6.00 equiv). The reaction mixture was stirred at room temperature for 2.5 h. The reaction was then quenched with saturated $NaHCO_3$ (50 mL) and the mixture extracted with Et_2O (3×50 mL). The collected organic layers were washed with brine, dried over Na_2SO_3 and concentrated in vacuo. The crude product was purified by flash column chromatography (9:1 hexane/Et_2O) to afford vicinal difluoride **58** (0.59 g, 2.7 mmol, 49%) as colorless liquid. TLC: R_f = 0.8 (7:3 hexane/EtOAc; UV, CAM); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.27 (m, 5H), 5.04–4.79 (m, 1H), 4.52 (s, 2H), 4.72–4.34 (m, 2H), 3.65–3.61 (m, 2H), 2.07–1.84 ppm (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.20, 128.60, 127.89, 127.79, 89.58 (dd, J = 172.4, 19.2 Hz), 84.44 (dd, J = 173.6, 22.0 Hz), 73.35, 30.74 ppm (dd, J = 21.1, 6.8 Hz); ^{19}F NMR (377 MHz, $CDCl_3$, decoupled): δ = −191.14 (d, J = 12.9 Hz, 1F), −229.87 ppm (d, J = 12.9 Hz, 1F); ^{19}F NMR (377 MHz, $CDCl_3$, not decoupled): δ = −190.91 - −191.37 (m, 1F), −229.87 ppm (tdd, J = 47.7, 22.3, 12.9 Hz, 1F); IR (neat): $\tilde{\nu}$ = 2958, 2866, 1496, 1454, 1363, 1096, 1027, 939, 897, 859, 736, 699, 668 cm^{-1}; HRMS (EI+) m/z: exact mass calculated for $C_{11}H_{13}F_2O$ [M-H]$^+$: 199.0934; found: 199.0929.

(*R*)-3,4-Difluorobutyl 4-nitrobenzenesulfonate (59): A solution of (*R*)-1-Benzyloxy-3,4-difluorobutane (**57**) (0.50 g, 2.5 mmol, 1.0 equiv) in 10 mL THF was added to a suspension of Pd/C (10 wt%) (0.32 g, 0.15 mmol, 0.060 equiv) in 2 mL THF. The reaction flask was flushed with nitrogen and one balloon of hydrogen gas. The reaction mixture was stirred at room temperature under a hydrogen atmosphere for 3 h then filtered through a pad of Celite and washed with 20 mL CH_2Cl_2. The filtrate was then treated with 4-nitrobenzene-1-sulfonyl chloride (0.79 g, 3.5 mmol, 1.4 equiv), Et_3N (0.70 mL, 5.0 mmol, 2.0 equiv) and DMAP (31 mg, 0.25 mmol, 0.10 equiv) and stirred for 2.5 h at room temperature. The reaction was then quenched with saturated NH_4Cl (40 mL) and the mixture extracted with EtOAc (3×20 mL). The collected organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (9:1 to 7:1 hexane/EtOAc) to give vicinal difluoride **59** (0.51, 1.7 mmol, 70%) as a light yellow solid. TLC: R_f = 0.40 (3:1 hexane/EtOAc; UV, $KMnO_4$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.42 (d, J = 9.1 Hz, 2H), 8.12 (d, J = 9.1 Hz, 2H), 4.90–4.25 (m, 5H), 2.23–1.96 ppm (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 151.05, 141.56, 129.41, 124.73, 87.68 (dd, J = 175.0, 20.0 Hz), 83.51 (dd, J = 175.4, 22.4 Hz), 66.96 (dd, J = 4.7, 1.1 Hz), 30.07 ppm (dd, J = 21.4, 6.9 Hz); ^{19}F NMR (377 MHz, $CDCl_3$, decoupled): δ = −193.68 (d, J = 12.5 Hz), −232.07 ppm (d, J = 12.5 Hz); ^{19}F NMR (377 MHz, $CDCl_3$, not decoupled): δ = −193.46 - −193.91 (m, 1F), −232.07 ppm (tdd, J = 47.3, 22.9, 12.4 Hz, 1F); IR (neat): $\tilde{\nu}$ = 3113, 1529, 1403, 1366, 1350, 1314, 1179, 1110, 1092, 1063, 970, 951, 924, 889, 854, 827, 792, 771, 736, 682 cm^{-1}; HRMS (ESI+) m/z: exact mass calculated for $C_{11}H_{11}F_2NNaO_5S$ [M]$^+$: 318.2018; found: 318.0217.

(*S*)-3,4-Difluorobutyl 4-nitrobenzenesulfonate (60): A solution of (*S*)-1-Benzyloxy-3,4-difluorobutane (**58**) (0.59 g, 2.7 mmol, 1.0 equiv) in 8 mL THF was added to a suspension of Pd/C (10 wt%) (0.28 g, 0.13 mmol, 0.050 equiv) in 2 mL THF. The reaction flask was flushed with nitrogen and one balloon of hydrogen gas. The reaction mixture was stirred at room temperature under a hydrogen atmosphere for 2 h then filtered through a pad of Celite and washed with 20 mL CH_2Cl_2. The filtrate was then treated with 4-nitrobenzene-1-sulfonyl chloride (0.85 g, 3.7 mmol, 1.4 equiv), Et_3N (0.75 mL, 5.4 mmol, 2.0 equiv) and DMAP (33 mg, 0.27 mmol, 0.10 equiv) and stirred for 4 h at room temperature. The reaction was then quenched with saturated NH_4Cl (40 mL) and the mixture extracted with EtOAc (3×20 mL). The collected organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (9:1 to 7:1 hexane/EtOAc) to give vicinal difluoride **60** (0.54, 1.8 mmol, 68%) as a light yellow solid. TLC: R_f = 0.40 (3:1 hexane/EtOAc; UV, $KMnO_4$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.42 (d, J = 9.1 Hz, 2H), 8.12 (d, J = 9.0 Hz, 2H), 4.91–4.26 (m, 5H), 2.22–1.97 ppm (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 151.07, 141.57, 129.41, 124.73, 87.68 (dd, J = 175.0, 20.0 Hz), 83.51 (dd, J = 175.4, 22.4 Hz), 66.95 (dd, J = 4.6, 1.1 Hz), 30.08 ppm (dd, J = 21.4, 6.9 Hz); ^{19}F NMR (377 MHz, $CDCl_3$, decoupled): δ = −193.69 (d, J = 12.5 Hz, 1F), −232.08 ppm (d, J = 12.5 Hz, 1F); ^{19}F NMR (377 MHz, $CDCl_3$, not decoupled): δ = −193.48–−193.90 (m, 1F), −232.08 ppm (tdd, J = 47.4, 22.9, 12.5 Hz, 1F); IR (neat): $\tilde{\nu}$ = 3118, 2975, 1529, 1368, 1350, 1315, 1293, 1180, 1118, 1093, 1064, 968, 951, 859, 827, 792, 747, 737, 683 cm^{-1}; HRMS (ESI+) m/z: exact mass calculated for $C_{11}H_{11}F_2NNaO_5S$ [M]$^+$: 318.2018; found: 318.0219.

(*S*)-*N*-(2,6-Dimethylphenyl)-1-((*R*)-2-hydroxybutyl)piperidine-2-carboxamide (63).[21] A solution of carboxamide **22** (0.80 g, 3.4 mmol, 1.0 equiv) in 5.3 mL MeCN was treated with lithium perchlorate (0.59 g, 5.4 mmol, 1.6 equiv) and (*R*)-2-ethyloxirane (**61**) (0.47 mL, 5.4 mmol, 1.6 equiv). The reaction was carried out in a sealed vessel stirring at 80 °C for 15 h. The reaction was quenched with saturated $NaHCO_3$ (40 mL) and the resulting mixture was extracted with EtOAc (3×40 mL). The collected organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (9:1 to 4:1 hexane/EtOAc) to give alcohol **63** (0.80 g, 2.6 mmol, 78%) as a white solid. TLC: R_f = 0.19 (9:1 CH_2Cl_2/acetone; UV, $KMnO_4$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (s, 1H), 7.11–7.02 (m, 3H), 3.83–3.74 (m, 1H), 3.26–3.19 (m, 1H), 3.00–2.93 (m, 1H), 2.82–2.69 (m, 1H), 2.32–2.26 (m, 1H), 2.24 (s, 6H), 2.20–2.11 (m, 1H), 2.09–1.99 (m, 1H), 1.87–1.77 (m, 1H), 1.77–1.68 (m, 2H), 1.63–1.29 (m, 4H), 0.97 ppm (t, J = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.44, 135.88, 133.81, 128.38, 127.38, 69.49, 68.46, 62.90, 52.21, 31.81, 28.16, 25.28, 23.82, 19.14, 10.20 ppm; IR (neat): $\tilde{\nu}$ = 3205, 2937, 2856, 2795, 1651, 1518, 1471, 1442, 1275, 1236, 1109, 1051, 989, 775, 711, 641 cm^{-1}; HRMS (ESI+) m/z: exact mass calculated for $C_{18}H_{29}N_2O_2$ [M+H]$^+$: 305.2224; found: 305.2228.

(*S*)-*N*-(2,6-Dimethylphenyl)-1-((*S*)-2-hydroxybutyl)piperidine-2-carboxamide (64).[21] A solution of carboxamide **22** (0.90 g, 3.8 mmol, 1.0 equiv) in 5.3 mL MeCN was treated with lithium perchlorate (0.44 g, 6.1 mmol, 1.6 equiv) and *rac*-2-ethyloxirane (**62**) (0.53 mL, 6.1 mmol, 1.6 equiv). The reaction was carried out in a sealed vessel stirring at 80 °C for 13 h. The reaction was quenched with saturated $NaHCO_3$ (40 mL) and the resulting mixture was extracted with EtOAc (3×40 mL). The collected organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo to obtain a crude mixture of epimers. The mixture was separated by flash column chromatography (9:1 to 4:1 hexane/EtOAc) to get the (2*S*,2′*S*) epimer **64** (0.61 g, 1.8 mmol, 47%) as a white solid. TLC: R_f = 0.10 (9:1 CH_2Cl_2/acetone; UV, $KMnO_4$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (s, 1H), 7.12–7.01 (m, 3H), 3.74–3.65 (m, 1H), 3.28–3.19 (m, 2H), 2.94–2.86 (m, 1H), 2.54–2.36 (m, 2H), 2.22 (s, 6H), 1.98–1.89 (m, 2H), 1.73–1.38 (m, 6H), 0.97 ppm (t, J = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.88, 135.36, 133.94, 128.37, 127.21, 70.85, 65.63, 61.69, 52.23, 28.38, 27.04, 23.59, 22.63, 18.95, 10.09 ppm; IR (neat): $\tilde{\nu}$ = 3479, 3262, 2914, 2850, 1650, 1601, 1460, 1441, 1071, 1031, 777, 738 cm^{-1}; HRMS (ESI+) m/z: exact mass calculated for $C_{18}H_{29}N_2O_2$ [M+H]$^+$: 305.2224; found: 305.2228.

(*S*)-Benzyl piperidine-2-carboxylate (66): To a solution of (*S*)-2-benzyl 1-*tert*-butyl piperidine-1,2-dicarboxylate (**65**)[22] (1.30 g,

4.07 mmol, 1.00 equiv) in 8 mL CH_2Cl_2 was slowly added TFA (1.92 mL, 24.4 mmol, 6.00 equiv), then the solution was stirred at room temperature for 12 h. The solvent was removed under reduced pressure and 10 mL of water were added. The pH of the mixture was brought into the range of 10–12 by the addition of 2 M NaOH, and the mixture was extracted with CH_2Cl_2 (5×40 mL). The combined organic phases were washed brine, dried over Na_2SO_4 and concentrated in vacuo to yield the product **66** (0.77 g, 3.5 mmol, 86%) as a colorless liquid. TLC: R_f=0.47 (9:1 CH_2Cl_2/MeOH; UV, $KMnO_4$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.40–7.28 (m, 5H), 5.18 (d, J=12.3 Hz, 1H), 5.13 (d, J=12.3 Hz, 1H), 3.40 (dd, J=9.9, 3.3 Hz, 1H), 3.08 (dt, J=12.0, 3.6 Hz, 1H), 2.65 (ddd, J=12.9, 10.0, 3.2 Hz, 1H), 2.02–1.89 (m, 2H), 1.83–1.72 (m, 1H), 1.62–1.51 (m, 2H), 1.51–1.36 ppm (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ= 173.56, 135.94, 128.70, 128.41, 128.35, 66.58, 58.82, 45.91, 29.38, 26.03, 24.22 ppm; IR (neat): $\tilde{\nu}$=2933, 2854, 1732, 1454, 1255, 1174, 1126, 1044, 1027, 966, 734 cm^{-1}; HRMS (ESI+) m/z: exact mass calculated for $C_{13}H_{18}NO_2$ $[M+H]^+$: 220.1332; found: 220.1329.

(*S*)-Benzyl 1-(2-oxopropyl)piperidine-2-carboxylate (67): To a stirring solution of (*S*)-benzyl piperidine-2-carboxylate (**66**) (1.91 g, 8.71 mmol, 1.00 equiv) in 10 mL MeCN was added K_2CO_3 (2.41 g, 17.4 mmol, 2.00 equiv) and chloroacetone (1.39 mL, 17.4 mmol, 2.00 equiv). The reaction mixture was stirred at room temperature for 24 h, and then diluted with 20 mL water. The mixture was extracted with EtOAc (3×20 mL), and the collected organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (4:1 to 3:1 hexane/EtOAc) to afford ketone **67** (2.06 g, 7.49 mmol, 86%) as a colorless oil. TLC: R_f=0.47 (9:1 CH_2Cl_2/MeOH; UV, $KMnO_4$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.39–7.28 (m, 5H), 5.17 (d, J=12.2 Hz, 1H), 5.10 (d, J=12.3 Hz, 1H), 3.42–3.37 (m, 1H), 3.36 (d, J=17.1 Hz, 1H), 3.16 (d, J=17.2 Hz, 1H), 2.94–2.87 (m, 1H), 2.43–2.35 (m, 1H), 2.09 (s, 3H), 1.94–1.79 (m, 2H), 1.64–1.57 (m, 2H), 1.57–1.48 (m, 1H), 1.47–1.37 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=208.08, 173.13, 135.92, 128.71, 128.45, 128.41, 66.29, 66.16, 63.59, 51.10, 29.43, 27.56, 25.41, 22.01 ppm; IR (neat): $\tilde{\nu}$=2937, 2855, 1727, 1711, 1454, 1352, 1213, 114, 1125, 1104, 1008, 966, 749, 697, 667 cm^{-1}; HRMS (ESI+) m/z: exact mass calculated for $C_{16}H_{22}NO_3$ $[M+H]^+$: 276.1594; found: 276.1594.

(*S*)-Benzyl 1-(2,2-difluoropropyl)piperidine-2-carboxylate (68): To a stirring solution of (*S*)-benzyl 1-(2-oxopropyl)piperidine-2-carboxylate (**67**) (1.90 g, 6.89 mmol, 1.00 equiv) in 23 mL CH_2Cl_2 was slowly added DAST (1.92 mL, 13.8 mmol, 2.00 equiv) at −5 °C. The reaction mixture was allowed to warm to room temperature over 4.5 h, then brought to 0 °C again and carefully quenched with saturated $NaHCO_3$ (50 mL). The mixture was extracted with EtOAc (3× 40 mL) and the collected organic layers washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (95:5 to 9:1 hexane/EtOAc) to afford geminal difluoride **68** (0.94 g, 3.2 mmol, 46%) as a yellow liquid. TLC: R_f=0.50 (9:1 hexane/EtOAc; UV, $KMnO_4$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.42–7.29 (m, 5H), 5.18 (d, J= 12.3 Hz, 1H), 5.13 (d, J=12.3 Hz, 1H), 3.52 (t, J=4.8 Hz, 1H), 3.17–3.09 (m, 1H), 2.94–2.75 (m, 2H), 2.58 (dt, J=11.3, 4.6 Hz, 1H), 2.02–1.92 (m, 1H), 1.87–1.77 (m, 1H), 1.64 (t, J=18.8 Hz, 3H), 1.61–1.44 (m, 3H), 1.37–1.25 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ= 173.38, 136.06, 128.73, 128.41, 128.33, 124.76 (t, J=239.3 Hz), 66.26, 63.60, 61.13 (t, J=28.9 Hz), 50.76, 29.23, 25.80, 21.56 (t, J= 26.6 Hz), 21.29 ppm; ^{19}F NMR (377 MHz, $CDCl_3$, decoupled): δ= −92.96 (d, J=255.49 Hz, 1F), −93.61 ppm (d, J=255.49 Hz, 1F); ^{19}F NMR (377 MHz, $CDCl_3$, not decoupled): δ=−92.51–−94.03 ppm (m, 2F); IR (neat): $\tilde{\nu}$=2936, 2854, 1730, 1454, 1391, 1241, 1190, 1156, 1113, 1096, 1066, 1009, 697, 629 cm^{-1}; HRMS (ESI+) m/z: exact mass calculated for $C_{16}H_{22}F_2NO_2$ $[M+H]^+$: 298.1611; found: 298.1611.

(*S*)-2-((*S*)-2-(Benzyloxy)-1-fluoroethyl)oxirane (73): Nonaflyl fluoride (1.76 mL, 9.42 mmol, 2.00 equiv) was added to a stirring solution of (2*R*,3*S*)-1-(benzyloxy)butane-2,3,4-triol (**69**)[23] (1.00 g, 4.71 mmol, 1.00 equiv) in 7.9 mL MeCN. The solution was then cooled to 0 °C and DBU (2.13 mL, 14.1 mmol, 3.00 equiv) was slowly added over a period of 10 min. After the addition, the reaction mixture was allowed to warm to room temperature and stirred for 1 h. The reaction was then quenched with saturated $NaHCO_3$ (30 mL) and the mixture was extracted with EtOAc (3× 40 mL). The collected organic layers were dried over Na_2SO_3 and concentrated in vacuo. The crude product was purified by flash column chromatography (9:1 to 4:1 hexane/EtOAc) to afford epifluorohydrin **73** (0.72 g, 3.5 mmol, 74%) as a colorless liquid. TLC: R_f=0.20 (6:1 hexane/EtOAc; UV, CAM); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.44–7.27 (m, 5H), 4.61 (s, 2H), 4.47 (dq, J=47.9, 5.1 Hz, 1H), 3.80–3.69 (m, 2H), 3.24 (dtd, J=13.4, 4.7, 2.6 Hz, 1H), 2.86 (app q, J=4.3 Hz, 1H), 2.75–2.71 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=137.67, 128.64, 128.05, 127.86, 92.10 (d, J=176.8 Hz), 73.86, 69.60 (d, J=24.9 Hz), 51.13 (d, J=24.0 Hz), 43.64 ppm (d, J= 8.9 Hz); ^{19}F NMR (377 MHz, $CDCl_3$, decoupled): δ=−195.78 ppm (s, 1F); ^{19}F NMR (377 MHz, $CDCl_3$, not decoupled): δ=−195.61 – −195.95 ppm (m, 1F); IR (neat): $\tilde{\nu}$=3028, 2944, 2866, 1453, 1365, 1253, 1205, 1096, 1027, 880, 737, 698 cm^{-1}; HRMS (EI+) m/z: exact mass calculated for $C_{11}H_{13}FO_2$ $[M]^+$: 196.0900; found: 196.0894.

(*R*)-2-((*R*)-2-(Benzyloxy)-1-fluoroethyl)oxirane (74): Nonaflyl fluoride (5.37 mL, 28.7 mmol, 2.20 equiv) was added to a stirring solution of (2*S*,3*R*)-1-(benzyloxy)butane-2,3,4-triol (**70**)[23] (2.77 g, 13.0 mmol, 1.00 equiv) in 65 mL MeCN. The solution was then cooled to 0 °C and DBU (6.62 mL, 43.1 mmol, 3.3 equiv) was slowly added over a period of 10 min. After the addition, the reaction mixture was allowed to warm to room temperature and stirred for 1 h. The reaction was then quenched with saturated $NaHCO_3$ (100 mL) and the mixture was extracted with EtOAc (3×80 mL). The collected organic layers were dried over Na_2SO_3 and concentrated in vacuo. The crude product was purified by flash column chromatography (9:1 to 4:1 hexane/EtOAc) to afford epifluorohydrin **74** (1.89 g, 9.63 mmol, 74%) as a colorless liquid. TLC R_f=0.20 (6:1 hexane/EtOAc; UV, CAM); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.40–7.27 (m, 5H), 4.61 (s, 2H), 4.47 (dq, J=47.9, 5.1 Hz, 1H), 3.80–3.69 (m, 2H), 3.28–3.19 (m, 1H), 2.88–2.83 (m, 1H), 2.76–2.71 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=137.70, 128.63, 128.02, 127.85, 91.46 (d, J=176.4 Hz), 73.81, 69.56 (d, J=22.2 Hz), 49.96 (d, J= 29.5 Hz), 45.18 ppm (d, J=4.9 Hz); ^{19}F NMR (377 MHz, $CDCl_3$, decoupled): δ=−195.78 ppm (s, 1F); ^{19}F NMR (377 MHz, $CDCl_3$, not decoupled): δ=−195.61–−195.95 ppm (m, 1F); IR (neat): $\tilde{\nu}$=3028, 2944, 2866, 1453, 1365, 1253, 1205, 1096, 1027, 880, 737, 698 cm^{-1}; HRMS (EI+) m/z: exact mass calculated for $C_{11}H_{13}FO_2$ $[M]^+$: 196.0900; found: 196.0894.

(*S*)-2-((*R*)-2-(Benzyloxy)-1-fluoroethyl)oxirane (75): Nonaflyl fluoride (2.61 mL, 13.9 mmol, 2.20 equiv) was added to a stirring solution of (2*R*,3*R*)-1-(benzyloxy)butane-2,3,4-triol (**71**)[24] (1.35 g, 6.34 mmol, 1.00 equiv) in 32 mL MeCN. The solution was then cooled to 0 °C and DBU (3.22 mL, 20.9 mmol, 3.30 equiv) was slowly added over a period of 10 min. After the addition, the reaction mixture was allowed to warm to room temperature and stirred for 1 h. The reaction was then quenched with saturated $NaHCO_3$ (60 mL) and the mixture was extracted with EtOAc (3× 50 mL). The collected organic layers were dried over Na_2SO_3 and concentrated in vacuo. The crude product was purified by flash

column chromatography (9:1 to 4:1 hexane/EtOAc) to afford epifluorohydrin **75** (0.82 g, 4.2 mmol, 66%) as a colorless liquid. TLC: R_f = 0.20 (6:1 hexane/EtOAc; UV, CAM); 1H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.27 (m, 5H), 4.61 (s, 2H), 4.58–4.42 (m, 1H), 3.79–3.71 (m, 2H), 3.20 (dddd, J = 10.0, 4.8, 4.0, 2.6 Hz, 1H), 2.87 (ddd, J = 5.0, 4.0, 1.7 Hz, 1H), 2.80 ppm (dd, J = 5.0, 2.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 137.70, 128.63, 128.02, 127.85, 91.46 (d, J = 176.4 Hz), 73.81, 69.56 (d, J = 22.2 Hz), 49.96 (d, J = 29.5 Hz), 45.18 ppm (d, J = 4.9 Hz); ^{19}F NMR (377 MHz, $CDCl_3$, decoupled): δ = −196.68 (s, 1F); 19F NMR (377 MHz, $CDCl_3$, not decoupled): δ = −196.68 ppm (dtdd, J = 48.1, 24.2, 10.0, 1.7 Hz); IR (neat): $\tilde{\nu}$ = 3064, 3031, 2933, 2865, 3003, 1454, 1115, 1097, 1047, 1027, 933, 884, 737 cm-1; HRMS (EI+) *m/z*: exact mass calculated for $C_{11}H_{13}FO_2$ [*M*]+: 196.0900; found: 196.0894.

(*R*)-2-((*S*)-2-(Benzyloxy)-1-fluoroethyl)oxirane (76): Nonaflyl fluoride (3.26 mL, 17.4 mmol, 2.50 equiv) was added to a stirring solution of (2*S*,3*S*)-1-(benzyloxy)butane-2,3,4-triol (**72**)[24] (1.48 g, 6.97 mmol, 1.00 equiv) in 35 mL MeCN. The solution was then cooled to 0 °C and DBU (3.75 mL, 24.4 mmol, 3.50 equiv) was slowly added over a period of 10 min. After the addition, the reaction mixture was allowed to warm to room temperature and stirred for 1 h. The reaction was then quenched with saturated $NaHCO_3$ (60 mL) and the mixture was extracted with EtOAc (3× 50 mL). The collected organic layers were dried over Na_2SO_3 and concentrated in vacuo. The crude product was purified by flash column chromatography (9:1 to 4:1 hexane/EtOAc) to afford epifluorohydrin **76** (0.78 g, 4.0 mmol, 57%) as a colorless liquid. TLC: R_f = 0.20 (6:1 hexane/EtOAc; UV, CAM); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.27 (m, 5H), 4.61 (s, 2H), 4.50 (dq, J = 48.2, 4.6 Hz, 1H), 3.79–3.70 (m, 2H), 3.23–3.17 (m, 1H), 2.89–2.78 ppm (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 137.70, 128.63, 128.02, 127.85, 91.46 (d, J = 176.4 Hz), 73.81, 69.56 (d, J = 22.3 Hz), 49.95 (d, J = 29.4 Hz), 45.18 ppm (d, J = 4.9 Hz); ^{19}F NMR (377 MHz, $CDCl_3$, decoupled): δ = −196.70 ppm (s, 1F); ^{19}F NMR (377 MHz, $CDCl_3$, not decoupled): δ = −196.70 ppm (dtd, J = 48.2, 24.0, 10.1 Hz, 1F); IR (neat): $\tilde{\nu}$ = 3031, 2939, 2865, 1496, 1453, 1366, 1251, 1205, 1098, 933, 883, 860, 738 cm^{-1}; HRMS (EI+) *m/z*: exact mass calculated for $C_{11}H_{13}FO_2$ [*M*]$^+$: 196.0900; found: 196.0894.

(2*S*,3*S*)-1-(Benzyloxy)-2-fluorobutan-3-ol (77): To a stirring suspension of LAH (64 mg, 1.6 mmol, 2.0 equiv) in 5 mL THF was added (*S*)-2-((*S*)-2-(benzyloxy)-1-fluoroethyl)oxirane (**73**) (0.16 g, 0.80 mmol, 1.0 equiv) in 2 mL THF at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h, then saturated NH_4Cl (10 mL) was carefully added and stirring was continued for another 10 min. The mixture was extracted with EtOAc (3×30 mL) and the collected organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (4:1 hexane/EtOAc) to afford fluorohydrin **77** (0.12 g, 0.63 mmol, 78%) as a colorless liquid. TLC: R_f = 0.33 (3:1 hexane/EtOAc; UV, CAM); ^{1}H NMR (400 MHz, $CDCl_3$): δ = ^{1}H NMR (400 MHz, Chloroform-d): δ = 7.40–7.27 (m, 5H), 4.61 (d, J = 12.0 Hz, 1H), 4.56 (d, J = 12.0 Hz, 1H), 4.42 (dtd, J = 47.8, 4.8, 3.5 Hz, 1H), 4.09–3.96 (m, 1H), 3.81–3.65 (m, 2H), 2.25 (brs, 1H), 1.24 ppm (dd, J = 6.5, 0.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 137.76, 128.74, 128.15, 128.01, 95.61 (d, J = 174.7 Hz), 73.95, 69.85 (d, J = 23.1 Hz), 67.50 (d, J = 20.2 Hz), 18.72 ppm (d, J = 5.5 Hz); ^{19}F NMR (377 MHz, $CDCl_3$, decoupled): δ = −200.10 ppm (s, 1F); ^{19}F NMR (377 MHz, $CDCl_3$, not decoupled): δ = −199.92–−200.28 ppm (m, 1F); IR (neat): $\tilde{\nu}$ = 3566, 2871, 1453, 1373, 1106, 1049, 884, 836, 739, 631 cm^{-1}; HRMS (EI+) *m/z*: exact mass calculated for $C_{11}H_{13}FO_2$ [*M*]$^+$: 198.1056; found: 198.1051.

(2*R*,3*R*)-1-(Benzyloxy)-2-fluorobutan-3-ol (78): To a stirring suspension of LAH (0.75 g, 19 mmol, 2.0 equiv) in 74 mL THF was added (*R*)-2-((*R*)-2-(benzyloxy)-1-fluoroethyl)oxirane (**74**) (1.85 g, 9.41 mmol, 1.00 equiv) in 20 mL THF at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h, then saturated NH_4Cl (100 mL) was carefully added and stirring was continued for another 10 min. The mixture was extracted with EtOAc (3×60 mL) and the collected organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (4:1 hexane/EtOAc) to afford fluorohydrin **78** (1.48 g, 7.47 mmol, 79%) as a colorless liquid. TLC: R_f = 0.33 (3:1 hexane/EtOAc; UV, CAM); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.27 (m, 5H), 4.61 (d, J = 12.0 Hz, 1H), 4.56 (d, J = 12.0 Hz, 1H), 4.42 (dtd, J = 47.8, 4.8, 3.5 Hz, 1H), 4.09–3.96 (m, 1H), 3.81–3.65 (m, 2H), 2.24 (brs, 1H), 1.24 (dd, J = 6.5, 0.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 137.66, 128.64, 128.05, 127.91, 95.51 (d, J = 174.7 Hz), 73.85, 69.75 (d, J = 23.1 Hz), 67.41 (d, J = 20.1 Hz), 18.62 (d, J = 5.5 Hz); ^{19}F NMR (377 MHz, $CDCl_3$, decoupled): δ = −200.11 (s, 1F); ^{19}F NMR (377 MHz, $CDCl_3$, not decoupled): δ = −199.93 - −200.29 (m, 1F); IR (neat): $\tilde{\nu}$ = 3410, 2977, 2935, 2869, 1453, 1373, 1256, 1105, 1053, 1027, 992, 880, 835, 737, 697, 612 cm^{-1}; HRMS (EI+) *m/z*: exact mass calculated for $C_{11}H_{13}FO_2$ [*M*]$^+$: 198.1056; found: 198.1051.

(2*R*,3*S*)-1-(Benzyloxy)-2-fluorobutan-3-ol (79): To a stirring suspension of LAH (0.32 g, 8.0 mmol, 2.0 equiv) in 20 mL THF was added (*S*)-2-((*R*)-2-(benzyloxy)-1-fluoroethyl)oxirane (**75**) (0.78 g, 4.0 mmol, 1.0 equiv) in 20 mL THF at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h, then saturated NH_4Cl (50 mL) was carefully added and stirring was continued for another 10 min. The mixture was extracted with EtOAc (3×40 mL) and the collected organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (4:1 hexane/EtOAc) to afford fluorohydrin **79** (0.62 g, 3.1 mmol, 79%) as a colorless liquid. TLC: R_f = 0.33 (3:1 hexane/EtOAc; UV, CAM); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.28 (m, 5H), 4.59 (s, 2H), 4.47 (dtd, J = 47.5, 5.3, 3.6 Hz, 1H), 4.10–3.98 (m, 1H), 3.84–3.68 (m, 2H), 2.16 (brs, 1H), 1.25 ppm (dd, J = 6.5, 1.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 137.68, 128.66, 128.07, 127.92, 94.96 (d, J = 174.6 Hz), 73.85, 69.25 (d, J = 23.3 Hz), 67.58 (dd, J = 23.2, 1.4 Hz), 18.61 ppm (d, J = 5.1 Hz); ^{19}F NMR (377 MHz, $CDCl_3$, decoupled): δ = −194.28 ppm (s, 1F); ^{19}F NMR (377 MHz, $CDCl_3$, not decoupled): δ = −194.08–−194.44 ppm (m, 1F); IR (neat): $\tilde{\nu}$ = 3411, 3065, 3303, 2977, 2934, 1453, 1090, 1058, 1028, 884, 667 cm^{-1}; HRMS (EI+) *m/z*: exact mass calculated for $C_{11}H_{13}FO_2$ [*M*]$^+$: 198.1056; found: 198.1051.

(2*S*,3*R*)-1-(Benzyloxy)-2-fluorobutan-3-ol (80): To a stirring suspension of LAH (0.23 g, 5.9 mmol, 2.0 equiv) in 15 mL THF was added (*R*)-2-((*S*)-2-(benzyloxy)-1-fluoroethyl)oxirane (**76**) (0.58 g, 2.9 mmol, 1.00 equiv) in 15 mL THF at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, then saturated NH_4Cl (50 mL) was carefully added and stirring was continued for another 10 min. The mixture was extracted with EtOAc (3×40 mL) and the collected organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (4:1 hexane/EtOAc) to afford fluorohydrin **80** (0.46 g, 2.3 mmol, 79%) as a colorless liquid. TLC: R_f = 0.33 (3:1 hexane/EtOAc; UV, CAM); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.28 (m, 5H), 4.59 (s, 2H), 4.47 (dtd, J = 47.5, 5.3, 3.5 Hz, 1H), 4.10–3.99 (m, 1H), 3.84–3.68 (m, 2H), 2.17 (brs, 1H), 1.25 ppm (dd, J = 6.7, 2.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 137.68, 128.66, 128.06, 127.91, 94.96 (d, J = 174.5 Hz), 73.84, 69.24 (d, J = 23.3 Hz), 67.56 (d, J = 23.4 Hz), 18.61 ppm (d, J = 5.1 Hz); ^{19}F NMR (377 MHz, $CDCl_3$, decoupled): δ = −194.24 ppm (s, 1F); ^{19}F NMR (377 MHz, $CDCl_3$, not decoupled): δ = −194.02 - −194.45 ppm (m, 1F); IR (neat): $\tilde{\nu}$ = 3409, 2977, 2934, 2869, 1453, 1369, 1257, 1206, 1093, 1058, 1028, 994, 884, 737, 697,

611 cm^{-1}; HRMS (EI+) *m/z*: exact mass calculated for $C_{11}H_{13}FO_2$ $[M]^+$: 198.1056; found: 198.1051.

(2*S*,3*R*)-1-Benzyloxy-2,3-difluorobutane (81): To a stirring solution of (2*S*,3*S*)-1-(benzyloxy)-2-fluorobutan-3-ol (**77**) (1.04 g, 4.77 mmol, 1.00 equiv) in 19 mL MeCN was sequentially added Et_3N (4.00 mL, 28.6 mmol, 6.00 equiv), triethylamine trihydrofluoride (1.64 mL, 9.55 mmol, 2.00 equiv) and nonaflyl fluoride (1.79 mL, 9.55 mmol, 2.00 equiv). The reaction mixture was stirred at room temperature for 2.5 h. The reaction was then quenched with saturated $NaHCO_3$ (30 mL) and the mixture extracted with Et_2O (3×30 mL). The collected organic phases were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (9:1 hexane/EtOAc) to afford vicinal difluoride **81** (0.82 g, 4.1 mmol, 86%) as a colorless liquid. TLC: R_f=0.55 (4:1 hexane/EtOAc; UV, $KMnO_4$); ^{1}H NMR (400 MHz, $CDCl_3$): 7.40–7.28 (m, 5H), 4.97–4.84 (m, 0.5H), 4.83–4.64 (m, 1H), 4.64–4.51 (m, 2.5H), 3.79–3.64 (m, 2H), 1.41 ppm (ddd, *J*=24.7, 6.5, 1.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=137.74, 128.62, 128.00, 127.84, 93.10 (dd, *J*=176.9, 25.2 Hz), 88.07 (dd, *J*=169.5, 25.3 Hz), 73.79, 68.38 (dd, *J*=22.3, 5.9 Hz), 16.33 ppm (dd, *J*=22.3, 5.2 Hz); ^{19}F NMR (377 MHz, $CDCl_3$, decoupled): δ=−185.67–−185.75 (m, 1F), −198.26 ppm (d, *J*=13.6 Hz, 1F); ^{19}F NMR (377 MHz, $CDCl_3$, not decoupled): δ=−185.45–−185.98 (m1 1F), −198.00–−198.50 ppm (m, 1F); IR (neat): $\tilde{\nu}$=2863, 1453, 1065, 995, 883, 837, 738, 699, 628 cm^{-1}; HRMS (EI+) *m/z*: exact mass calculated for $C_{11}H_{14}F_2O$ $[M]^+$: 200.1013; found: 200.1008.

(2*R*,3*S*)-1-Benzyloxy-2,3-difluorobutane (82): To a stirring solution of (2*R*,3*R*)-1-benzyloxy-2-fluorobutan-3-ol (**78**) (1.45 g, 7.33 mmol, 1.00 equiv) in 29 mL MeCN was sequentially added Et_3N (6.13 mL, 44.0 mmol, 6.00 equiv), triethylamine trihydrofluoride (2.51 mL, 14.7 mmol, 2.00 equiv) and nonaflyl fluoride (2.87 mL, 14.7 mmol, 2.00 equiv). The reaction mixture was stirred at room temperature for 3.5 h. The reaction was then quenched with saturated $NaHCO_3$ (30 mL) and the mixture extracted with Et_2O (3×30 mL). The collected organic phases were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (9:1 hexane/EtOAc) to afford vicinal difluoride **82** (1.17 g, 5.83 mmol, 80%) as a colorless liquid. TLC: R_f=0.55 (4:1 hexane/EtOAc; UV, $KMnO_4$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.39–7.28 (m, 5H), 4.94–4.83 (m, 0.5H), 4.82–4.64 (m, 1H), 4.64–4.53 (m, 2.5H), 3.77–3.73 (m, 1H), 3.70–3.67 (m, 1H), 1.41 ppm (ddd, *J*=24.7, 6.4, 1.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=137.74, 128.63, 128.01, 127.85, 93.10 (dd, *J*=176.9, 25.2 Hz), 88.07 (dd, *J*=169.5, 25.3 Hz), 73.79, 68.38 (dd, *J*=22.3, 5.9 Hz), 16.34 ppm (dd, *J*=22.2, 5.2 Hz); ^{19}F NMR (377 MHz, $CDCl_3$, decoupled): δ=−185.71 (d, *J*=13.6, 1F), −198.26 ppm (d, *J*=13.6 Hz, 1F); ^{19}F NMR (377 MHz, $CDCl_3$, not decoupled): δ=−185.50 - −185.93 (m, 1F), −198.07–−198.46 ppm (m, 1F); IR (neat): $\tilde{\nu}$=2949, 2867, 1453, 1365, 1090, 1064, 1028, 883, 838, 737, 697 cm^{-1}; HRMS (EI+) *m/z*: exact mass calculated for $C_{11}H_{14}F_2O$ $[M]^+$: 200.1013; found: 200.1008.

(2*R*,3*R*)-1-Benzyloxy-2,3-difluorobutane (83): To a stirring solution of (2*R*,3*S*)-1-(benzyloxy)-2-fluorobutan-3-ol (**79**) (0.63 g, 3.2 mmol, 1.0 equiv) in 12.8 mL MeCN was sequentially added Et_3N (2.67 mL, 19.2 mmol, 6.00 equiv), triethylamine trihydrofluoride (1.10 mL, 6.39 mmol, 2.00 equiv) and nonaflyl fluoride (1.25 mL, 6.39 mmol, 2.00 equiv). The reaction mixture was stirred at room temperature for 1 h. The reaction was then quenched with saturated $NaHCO_3$ (10 mL) and the mixture extracted with Et_2O (3×20 mL). The collected organic phases were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (9:1 hexane/EtOAc) to afford vicinal difluoride **83** (0.57 g, 2.8 mmol, 89%) as a colorless liquid. TLC: R_f=0.55 (4:1 hexane/EtOAc; UV, $KMnO_4$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.39–7.28 (m, 5H), 4.96–4.72 (m, 1H), 4.58 (s, 2H), 4.68–4.42 (m, 1H), 3.78–3.69 (m, 2H), 1.40 ppm (ddd, *J*=24.1, 6.5, 0.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=137.69, 128.64, 128.05, 127.91, 93.16 (dd, *J*=179.2, 19.7 Hz), 88.46 (dd, *J*=172.4, 20.5 Hz), 73.84, 68.61 (dd, *J*=24.5, 7.1 Hz), 16.31 ppm (dd, *J*=22.8, 6.5 Hz); ^{19}F NMR (377 MHz, $CDCl_3$, decoupled): δ=−190.73 (d, *J*=11.0 Hz, 1F), −201.55 ppm (d, *J*=11.0 Hz, 1F); ^{19}F NMR (377 MHz, $CDCl_3$, not decoupled): δ=−190.51 - −190.96 (m), −201.55 ppm (dqd, *J*=46.8, 21.3, 11.0 Hz); IR (neat): $\tilde{\nu}$=3032, 3065, 2989, 2940, 1454, 1113, 1097, 1049, 1027, 737, 687 cm^{-1}; HRMS (EI+) *m/z*: exact mass calculated for $C_{11}H_{14}F_2O$ $[M]^+$: 200.1013; found: 200.1008.

(2*S*,3*S*)-1-Benzyloxy-2,3-difluorobutane (84): To a stirring solution of (2*S*,3*R*)-1-(benzyloxy)-2-fluorobutan-3-ol (**80**) (0.48 g, 2.2 mmol, 1.0 equiv) in 8.9 mL MeCN was sequentially added Et_3N (1.86 mL, 13.4 mmol, 6.00 equiv), triethylamine trihydrofluoride (0.76 mL, 4.5 mmol, 2.0 equiv) and nonaflyl fluoride (0.83 mL, 4.5 mmol, 2.0 equiv). The reaction mixture was stirred at room temperature for 1 h. The reaction was then quenched with saturated $NaHCO_3$ (10 mL) and the mixture was extracted with Et_2O (3×20 mL). The collected organic phases were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (9:1 hexane/EtOAc) to afford vicinal difluoride **84** (0.37 g, 1.9 mmol, 84%) as a colorless liquid. TLC: R_f=0.55 (4:1 hexane/EtOAc; UV, $KMnO_4$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.39–7.28 (m, 5H), 4.96–4.72 (m, 1H), 4.59 (s, 2H), 4.65–4.44 (m, 1H), 3.78–3.70 (m, 2H), 1.40 ppm (dd, *J*=24.0, 6.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=137.68, 128.63, 128.05, 127.91, 93.16 (dd, *J*=179.3, 19.7 Hz), 88.45 (dd, *J*=172.4, 20.4 Hz), 73.84, 68.60 (dd, *J*=24.5, 7.1 Hz), 16.31 ppm (dd, *J*=22.8, 6.5 Hz); ^{19}F NMR (377 MHz, $CDCl_3$, decoupled): δ=−190.69–−190.75 (m, 1F), −201.50–−201.58 ppm (m, 1F); ^{19}F NMR (377 MHz, $CDCl_3$, not decoupled): δ=−190.50–−190.95 (m, 1F), −201.35–−201.73 ppm (m, 1F); IR (neat): $\tilde{\nu}$=3032, 2989, 2869, 1497, 1454, 1384, 1364, 1206, 1153, 1114, 1063, 1049, 1027, 981, 918, 880, 826, 737, 697, 675, 611 cm^{-1}; HRMS (EI+) *m/z*: exact mass calculated for $C_{11}H_{14}F_2O$ $[M]^+$: 200.1013; found: 200.1008.

(2*S*,3*R*)-2,3-Difluorobutyl 4-nitrobenzenesulfonate (85): (2*S*,3*R*)-1-Butyloxy-2,3-difluorobutane (**81**) (0.86 g, 3.9 mmol, 1.0 equiv) was added to a suspension of Pd/C (10 wt%) (0.21 g, 0.19 mmol, 0.10 equiv) in 9 mL THF. The reaction flask was flushed with nitrogen and one balloon of hydrogen gas. The reaction mixture was stirred at room temperature under a hydrogen atmosphere for 1 h then filtered through a pad of Celite and washed with 10 mL CH_2Cl_2. The filtrate was then treated with 4-nitrobenzene-1-sulfonyl chloride (1.23 g, 5.43 mmol, 1.40 equiv), Et_3N (1.08 mL, 7.76 mmol, 2.00 equiv) and DMAP (47 mg, 0.39 mmol, 0.10 equiv) and stirred for 1 h at room temperature. The reaction was then quenched with saturated NH_4Cl (40 mL) and the mixture extracted with EtOAc (3×30 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (4:1 to 3:2 hexane/EtOAc) to give vicinal difluoride **85** (0.84 g, 2.8 mmol, 73%) as a light yellow solid. TLC: R_f=0.55 (4:1 hexane/EtOAc; UV, $KMnO_4$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.45–8.38 (m, 2H), 8.16–8.10 (m, 9H), 4.80 (dp, *J*=9.4, 6.4 Hz, 0.5H), 4.73–4.58 (m, 1H), 4.54–4.28 (m, 2.5H), 1.41 ppm (ddd, *J*=24.7, 6.4, 1.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=151.08, 141.39, 129.48, 124.68, 90.79 (dd, *J*=181.0, 26.9 Hz), 86.85 (dd, *J*=171.0, 26.5 Hz), 68.51 (dd, *J*=22.0, 5.4 Hz), 16.97 ppm (dd, *J*=21.8, 3.9 Hz); ^{19}F NMR (377 MHz, $CDCl_3$, decoupled): δ=−187.90 (d, *J*=14.9 Hz, 1F), −196.57 ppm (d, *J*=14.7 Hz, 1F); ^{19}F NMR (377 MHz, $CDCl_3$, not decoupled): δ=^{19}F NMR −187.69–−188.11 (m, 1F),

−196.38–−196.76 ppm (m, 1F); IR (neat): $\tilde{\nu}$ = 3110, 1530, 1368, 1352, 1308, 1188, 1173, 1092, 1070, 1038, 954, 889, 879, 855, 779, 746, 737, 682 cm^{-1}; HRMS (ESI+) *m/z*: exact mass calculated for $C_{10}H_{11}F_2NNaO_5S$ $[M+Na]^+$: 318.0218; found: 318.0218.

(2*R*,3*S*)-2,3-Difluorobutyl 4-nitrobenzenesulfonate (86): (2*R*,3*S*)-1-Benzyloxy-2,3-difluorobutane (**82**) (1.12 g, 5.59 mmol, 1.00 equiv) was added to a suspension of Pd/C (10 wt%) (0.59 g, 0.56 mmol, 0.10 equiv) in 20 mL THF. The reaction flask was flushed with nitrogen and one balloon of hydrogen gas. The reaction mixture was stirred at room temperature under a hydrogen atmosphere for 6 h then filtered through a pad of Celite and washed with 10 mL CH_2Cl_2. The filtrate was then treated with 4-nitrobenzene-1-sulfonyl chloride (1.90 g, 8.39 mmol, 1.50 equiv), Et_3N (1.56 mL, 11.2 mmol, 2.00 equiv) and DMAP (68 mg, 0.56 mmol, 0.10 equiv) and stirred for 1.5 h at room temperature. The reaction was then quenched with saturated NH_4Cl (30 mL) and the mixture extracted with EtOAc (3×20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (4:1 to 3:2 hexane/EtOAc) to give vicinal difluoride **86** (0.93 g, 3.1 mmol, 56%) as a light yellow solid. TLC: R_f = 0.55 (4:1 hexane/EtOAc; UV $KMnO_4$; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.45–8.38 (m, 2H), 8.16–8.10 (m, 9H), 4.80 (dp, *J* = 9.4, 6.4 Hz, 0.5H), 4.73–4.58 (m, 1H), 4.54–4.28 (m, 2.5H), 1.41 ppm (ddd, *J* = 24.7, 6.4, 1.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 151.08, 141.39, 129.48, 124.68, 90.79 (dd, *J* = 181.0, 26.9 Hz), 86.85 (dd, *J* = 171.0, 26.5 Hz), 68.51 (dd, *J* = 22.0, 5.4 Hz), 16.97 ppm (dd, *J* = 21.8, 3.9 Hz); ^{19}F NMR (377 MHz, $CDCl_3$, decoupled): δ = −187.90 (d, *J* = 14.9 Hz, 1F), −196.57 ppm (d, *J* = 14.7 Hz, 1F); ^{19}F NMR (377 MHz, $CDCl_3$, not decoupled): δ = −187.69–−188.11 (m, 1F), −196.38–−196.76 ppm (m, 1F); IR (neat): $\tilde{\nu}$ = 3110, 1530, 1368, 1352, 1308, 1188, 1173, 1092, 1070, 1038, 954, 889, 879, 855, 779, 746, 737, 682 cm^{-1}; HRMS (ESI+) *m/z*: exact mass calculated for $C_{10}H_{11}F_2NNaO_5S$ $[M+Na]^+$: 318.0218; found: 318.0218.

(2*R*,3*R*)-2,3-Difluorobutyl 4-nitrobenzenesulfonate (87): (2*R*,3*R*)-1-Benzyloxy-2,3-difluorobutane (**83**) (0.54 g, 2.7 mmol, 1.0 equiv) was added to a suspension of Pd/C (10 wt%) (0.28 g, 0.27 mmol, 0.10 equiv) in 13.4 mL THF. The reaction flask was flushed with nitrogen and one balloon of hydrogen gas. The reaction mixture was stirred at room temperature under a hydrogen atmosphere for 6 h then filtered through a pad of Celite and washed with 10 mL CH_2Cl_2. The filtrate was then treated with 4-nitrobenzene-1-sulfonyl chloride (0.91 g, 4.0 mmol, 1.5 equiv), Et_3N (0.75 mL, 5.4 mmol, 2.0 equiv) and DMAP (33 mg, 0.27 mmol, 0.10 equiv) and stirred for 1.5 h at room temperature. The reaction was then quenched with saturated NH_4Cl (40 mL) and the mixture extracted with EtOAc (3× 30 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (4:1 to 3:2 hexane/EtOAc) to give vicinal difluoride **87** (0.21 g, 0.71 mmol, 27%) as a light yellow solid. TLC: R_f = 0.55 (4:1 hexane/EtOAc; UV, $KMnO_4$); ^1H NMR (400 MHz, $CDCl_3$): δ = 8.46–8.40 (m, 2H), 8.16–8.10 (m, 2H), 4.88–4.51 (m, 2H), 4.44–4.33 (m, 2H), 1.42 ppm (ddd, *J* = 24.1, 6.6, 1.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 141.30, 129.51, 124.72, 90.58 (dd, *J* = 184.2, 20.4 Hz), 87.50 (dd, *J* = 174.7, 20.5 Hz), 68.84 (dd, *J* = 25.9, 7.9 Hz), 15.98 ppm (dd, *J* = 22.7, 6.2 Hz); ^{19}F NMR (377 MHz, $CDCl_3$, decoupled): δ = −191.96 (d, *J* = 9.9 Hz, 1F), −204.23 ppm (d, *J* = 9.9 Hz, 1F); ^{19}F NMR (377 MHz, $CDCl_3$, not decoupled): δ = −191.95 (dpd, *J* = 47.6, 23.9, 9.9 Hz), −204.23 ppm (dqd, *J* = 47.2, 21.8, 9.7 Hz); IR (neat): $\tilde{\nu}$ = 3117, 3103, 3074, 3004, 2949, 1407, 1369, 1351, 1181, 1155, 1092, 1058, 980, 880, 860, 848, 794, 745, 737, 681 cm^{-1}; HRMS (ESI+) *m/z*: exact mass calculated for $C_{10}H_{11}F_2NNaO_5S$ $[M+Na]^+$: 318.0218; found: 318.0217.

(2*S*,3*S*)-2,3-Difluorobutyl 4-nitrobenzenesulfonate (88): (2*S*,3*S*)-1-Benzyloxy-2,3-difluorobutane (**84**) (0.37 g, 1.72 mmol, 1.00 equiv) was added to a suspension of Pd/C (10 wt%) (0.19 g, 0.18 mmol, 0.10 equiv) in 9 mL THF. The reaction flask was flushed with nitrogen and one balloon of hydrogen gas. The reaction mixture was stirred at room temperature under a hydrogen atmosphere for 3.5 h then filtered through a pad of Celite and washed with 10 mL CH_2Cl_2. The filtrate was then treated with 4-nitrobenzene-1-sulfonyl chloride (0.57 g, 2.51 mmol, 1.40 equiv), Et_3N (0.50 mL, 3.58 mmol, 2.00 equiv) and DMAP (22 mg, 0.18 mmol, 0.10 equiv) and stirred for 1 h at room temperature. The reaction was then quenched with saturated NH_4Cl (40 mL) and the mixture extracted with EtOAc (3×30 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (4:1 to 3:2 hexane/EtOAc) to give vicinal difluoride **88** (0.37 g, 1.2 mmol, 69%) as a light yellow solid. TLC: R_f = 0.55 (4:1 hexane/EtOAc; UV, $KMnO_4$); ^1H NMR (400 MHz, $CDCl_3$): δ = 8.45–8.40 (m, 2H), 8.16–8.10 (m, 2H), 4.88–4.51 (m, 2H), 4.43–4.34 (m, 2H), 1.42 ppm (ddd, *J* = 24.1, 6.5, 1.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 151.12, 141.30, 129.51, 124.72, 90.58 (dd, *J* = 184.2, 20.3 Hz), 87.50 (dd, *J* = 174.6, 20.5 Hz), 68.84 (dd, *J* = 25.9, 7.9 Hz), 15.98 ppm (dd, *J* = 22.8, 6.1 Hz); ^{19}F NMR (377 MHz, $CDCl_3$, decoupled): δ = −191.95 (d, *J* = 9.8 Hz, 1F), −204.23 ppm (d, *J* = 9.8 Hz, 1F); ^{19}F NMR (377 MHz, $CDCl_3$, not decoupled): δ = −191.72–−192.18 (m), −204.04–−204.46 ppm (m); IR (neat): $\tilde{\nu}$ = 3117, 3104, 1612, 1540, 1407, 1370, 1350, 1318, 1295, 1183, 1154, 1092, 1058, 1002, 848, 792, 744, 680, 617 cm^{-1}; HRMS (ESI+) *m/z*: exact mass calculated for $C_{10}H_{15}F_2N_2O_5S$ $[M+NH_4]^+$: 313.0664; found: 313.0665.

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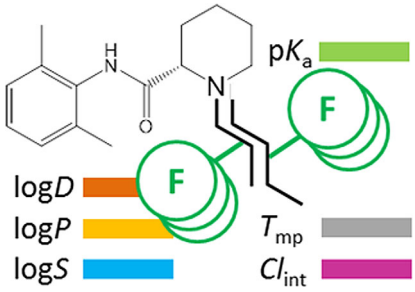
Fine tuned in F sharp: Fluorinated *N*-alkyl-piperidine-2-carboxamides display remarkably consistent response of pharmacologically relevant properties to variations of the fluorination pattern in the alkyl group. Compared to neutral alkyl-substituted heteroaryl systems, characteristic deviations of response to fluorination are observed due to strong modulation of amine basicity affecting lipophilicity and other pharmacologically relevant properties.



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Effect of Partially Fluorinated *N*-Alkyl-Substituted Piperidine-2-carboxamides on Pharmacologically Relevant Properties